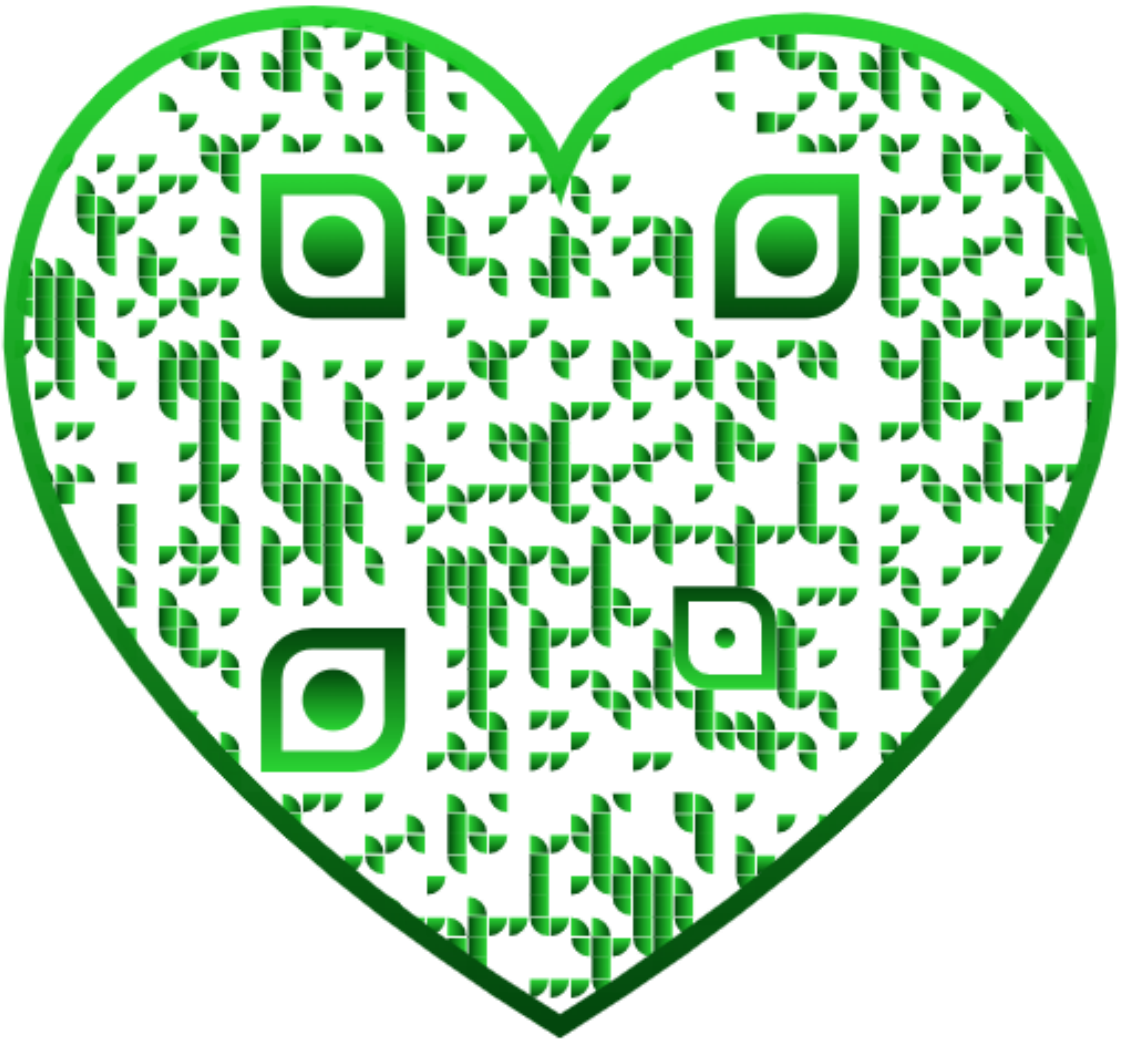
ANTIBIOTICS COURSE

Prepared by :

Dr. Waleed Al-Sibakhi



Introduction to Antibiotics:

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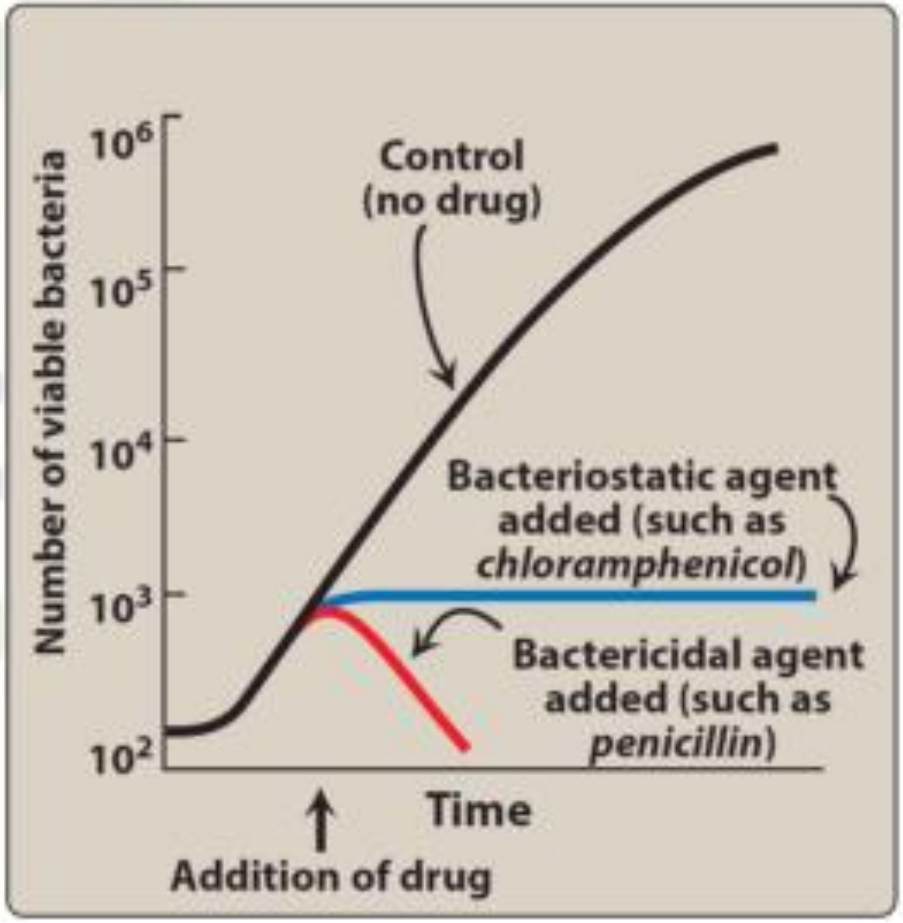
Antibiotics

Are drugs that act against bacteria , by one of the following manners:

1) Killing Bacteria **(bacteri-cidals).**

2) Inhibition of bacterial replication **(bacterio-statics)** allowing the immune system to kill the bacteria !!



Classification of Antibiotics according to the Spectrum of activity:

1) Narrow-spectrum antibiotics:

Act against single type or limited types of bacteria, e.g. Isoniazid and Penicillin G.

2) Extended-spectrum antibiotics:

Act against more types of bacteria, e.g. Amoxicillin.

3) Broad-spectrum antibiotics:

Act against more and more types of bacteria, e.g. Amoxicillin + clavulanate.

Types of therapy with antibiotics:

1) Definitive Therapy:

Choose the antibiotic that is proved to be effective according to the **"antibiotic sensitivity test".**

The Inhibition Zone

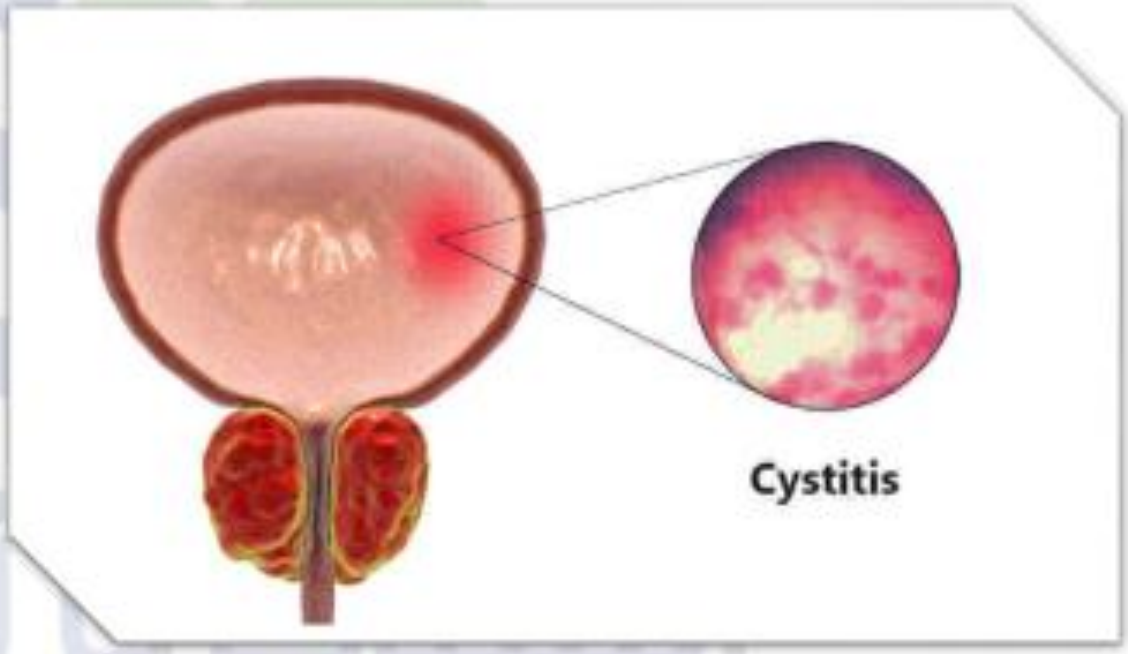
Name of the antimicrobial agents	Sensitivity
Amoxycillin	R
Nitofurantoin	S
Cephotaxime	I
Enrofloxacin	R
Ceftriaxone	S
Streptomycin	S
Amikacin	I
Tetramycin	R
Chloramphenicol	S
Ciprofloxacin	R
Penicillin	R
Nalidixic Acid	R
Ampicillin	

But check the Pharmaco-kinetics

2) Empirical Therapy:

We choose the antibiotic that is expected to be effective against the "causative bacteria" of this infection, according to the **"Guidelines".**

- **Disease:** sore throat.
- **Bacteria:** Strep. pyogenes.
- **Antibiotic:** **Penicillin V.**

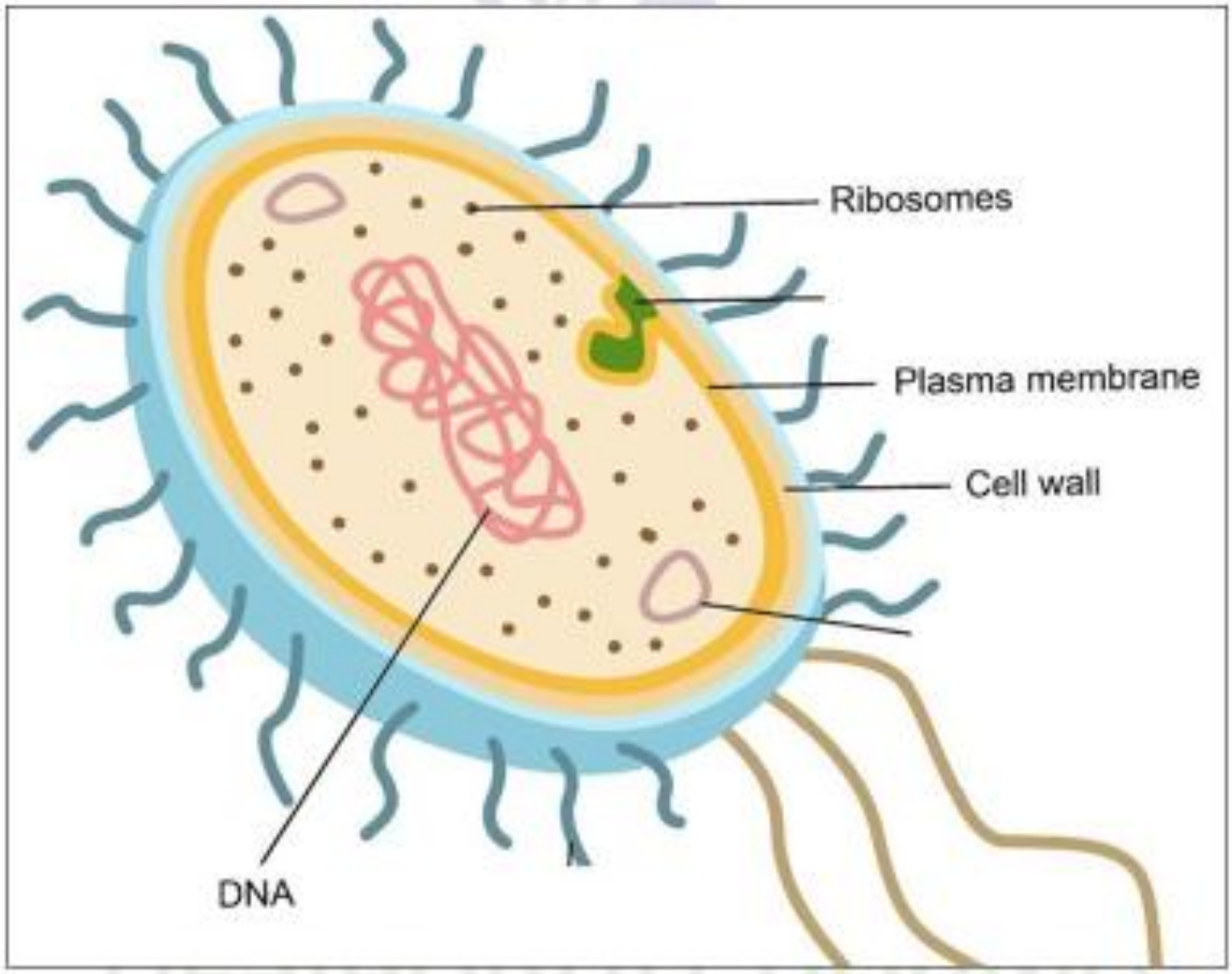


- **Disease:** cystitis (uncomplicated, in women.
- **Bacteria:** E. coli
- **Antibiotic:** **Nitrofurantoin, Fosfomycin.**

- **Disease:** bacterial sinusitis.
- **Bacteria:** Streptococcus pneumoniae, Hemophilus influenzae, Moraxella catarrhalis, and Streptococcus pyogenes.
- **Antibiotic:** Augmentin, doxycycline.

- **Disease:** Diabetic foot
- **Bacteria:** Staphylococcus aureus, S. saprophyticus, S. epididermis, Streptococcus pyogenes, S. mutans, Pseudomonas aeruginosa, Bacillus subtilis, Proteus species, E. coli and Klebsiella pneumoniae.
- **Antibiotic:** Cefepime.

Classification of Antibiotics according to M.O.A:

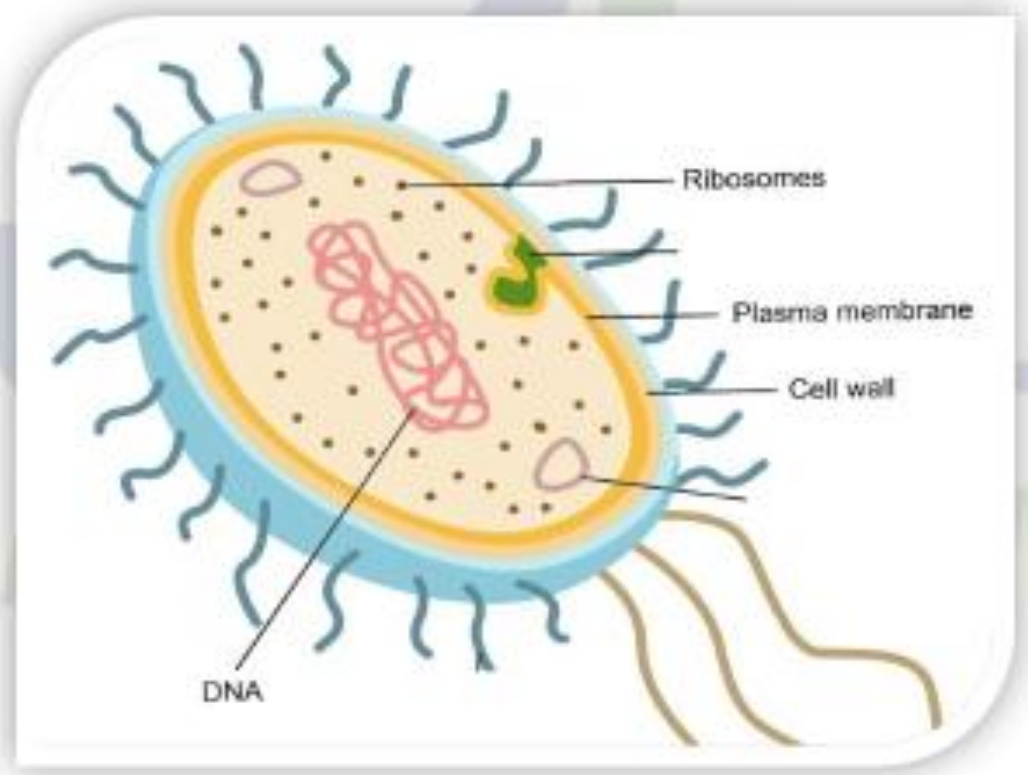


1) Cell-wall inhibitors.

2) Cell-membrane disrupters.

3) Protein-synthesis inhibitors.

4) Nucleic acid-synthesis inhibitors.

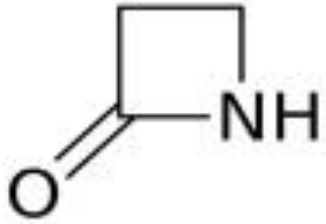


Bacterial resistance:

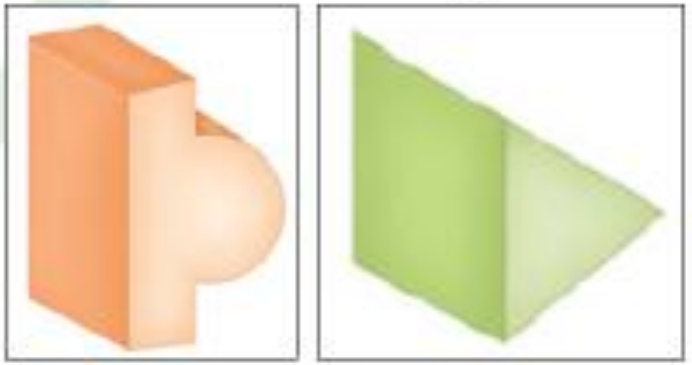
Incorrect use of antibiotics is main cause of bacterial resistance (incorrect drug, incorrect dose, incorrect frequency, incorrect duration or incorrect administration).

This leads to a change in bacterial DNA (mutation) that leads to:

1) Enzyme secretion, e.g. **β**-lactamase enzymes.



2) Change of drug binding-site.



3) ↓ Drug influx (↓ permeability).

4) ↑ Drug efflux.

5) Change of bacterial substrate, e.g. change of PABA.

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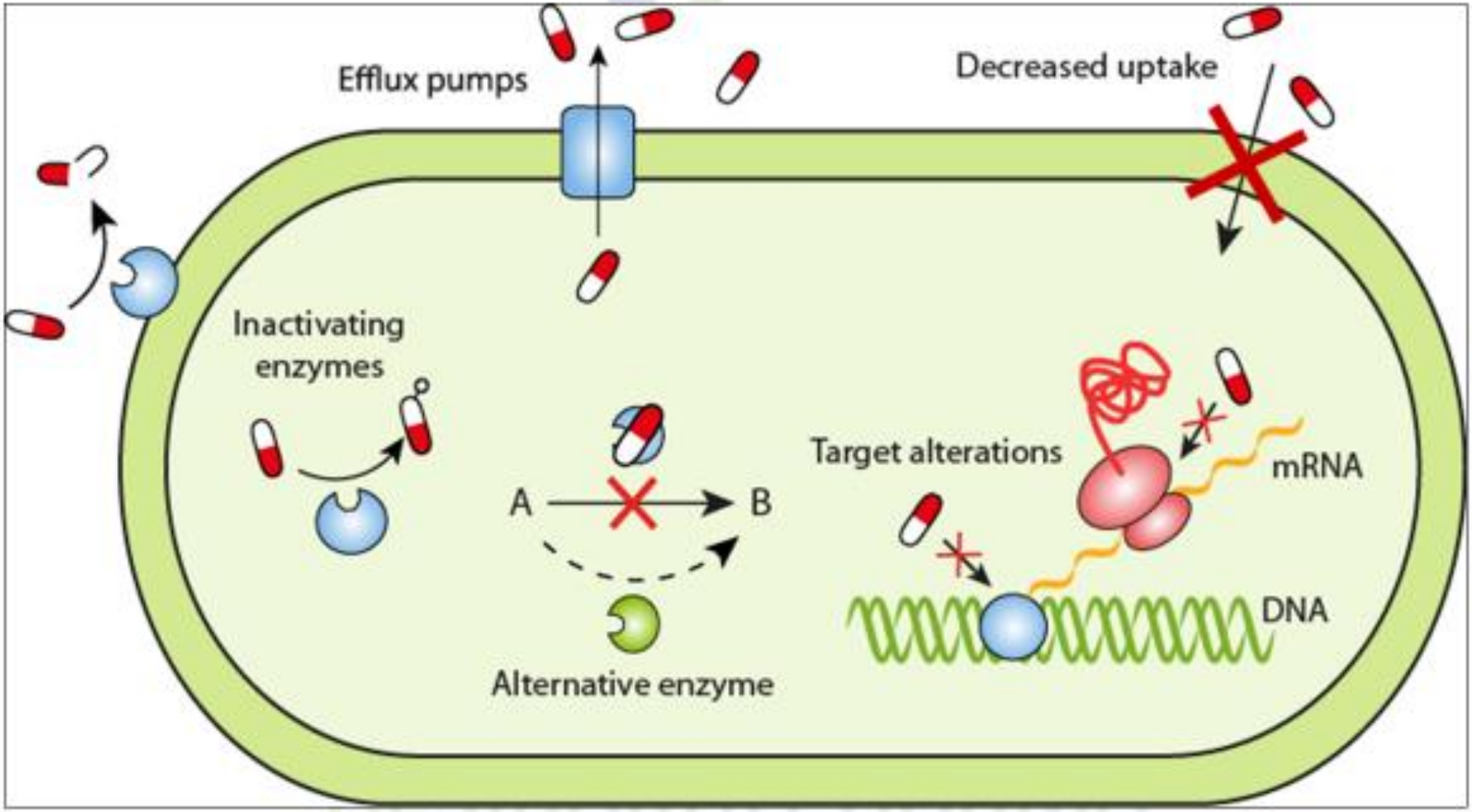
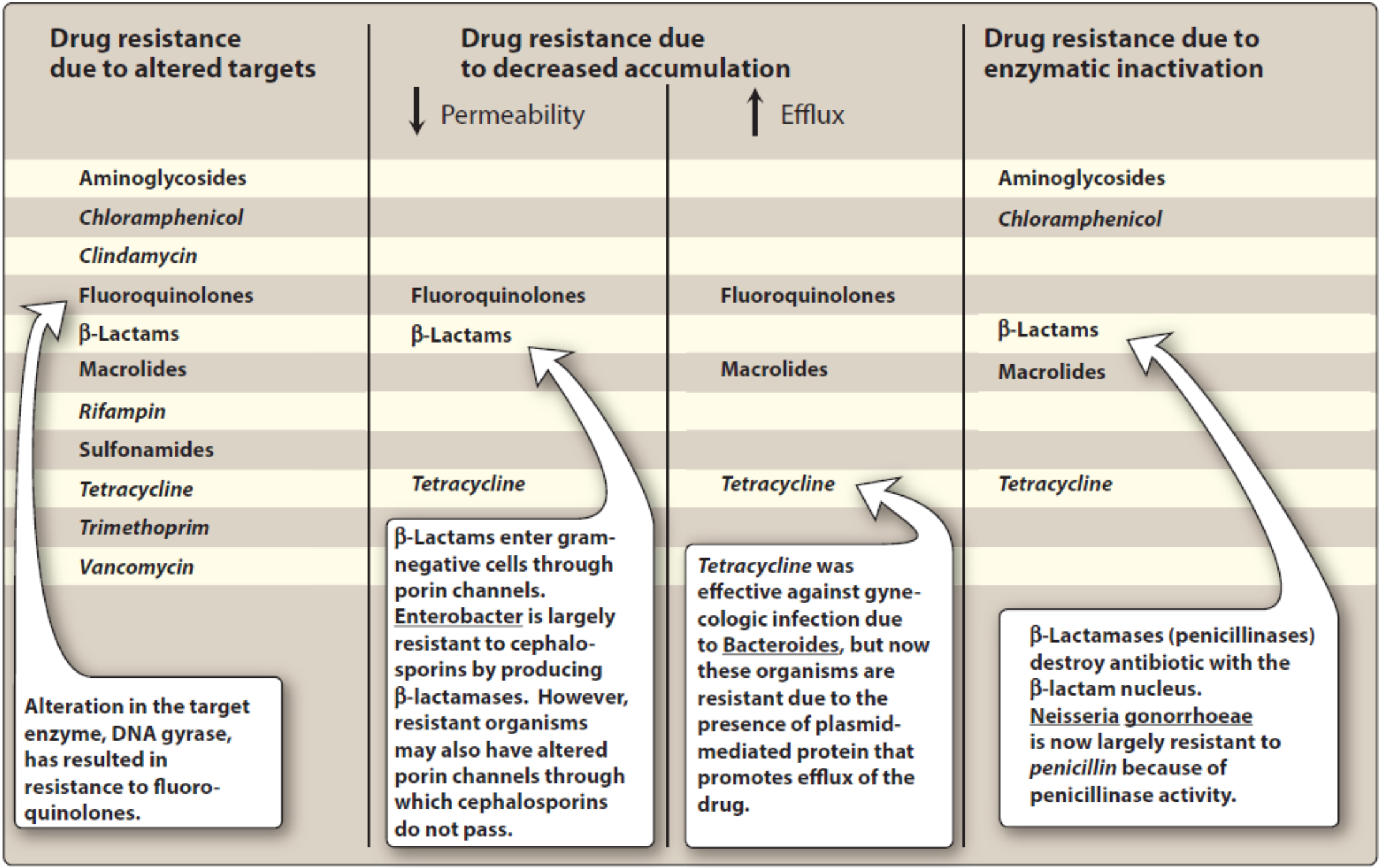
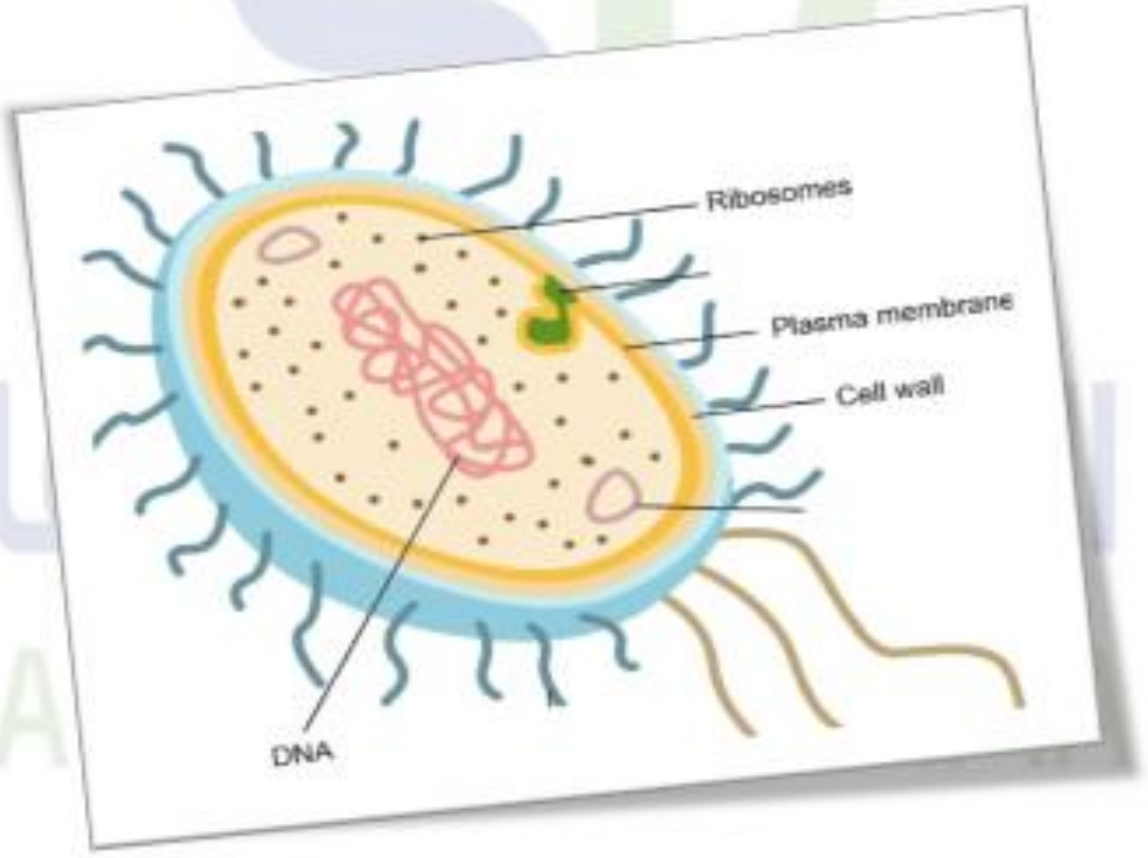

Efflux pumps
Decreased uptake
Inactivating enzymes
A
B
Alternative enzyme
Target alterations
mRNA
DNA


Drug resistance due to altered targets
Drug resistance due to decreased accumulation
Permeability
Efflux
Drug resistance due to enzymatic inactivation
Aminoglycosides
Chloramphenicol
Clindamycin
Fluoroquinolones
β-Lactams
Macrolides
Rifampin
Sulfonamides
Tetracycline
Trimethoprim
Vancomycin
Fluoroquinolones
β-Lactams
Tetracycline
Fluoroquinolones
Macrolides
Tetracycline
Aminoglycosides
Chloramphenicol
β-Lactams
Macrolides
Tetracycline
Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoroquinolones.
β-Lactams enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalosporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which cephalosporins do not pass.
Tetracycline was effective against gynecologic infection due to Bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.
β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to penicillin because of penicillinase activity.

1) Cell Wall Inhibitions

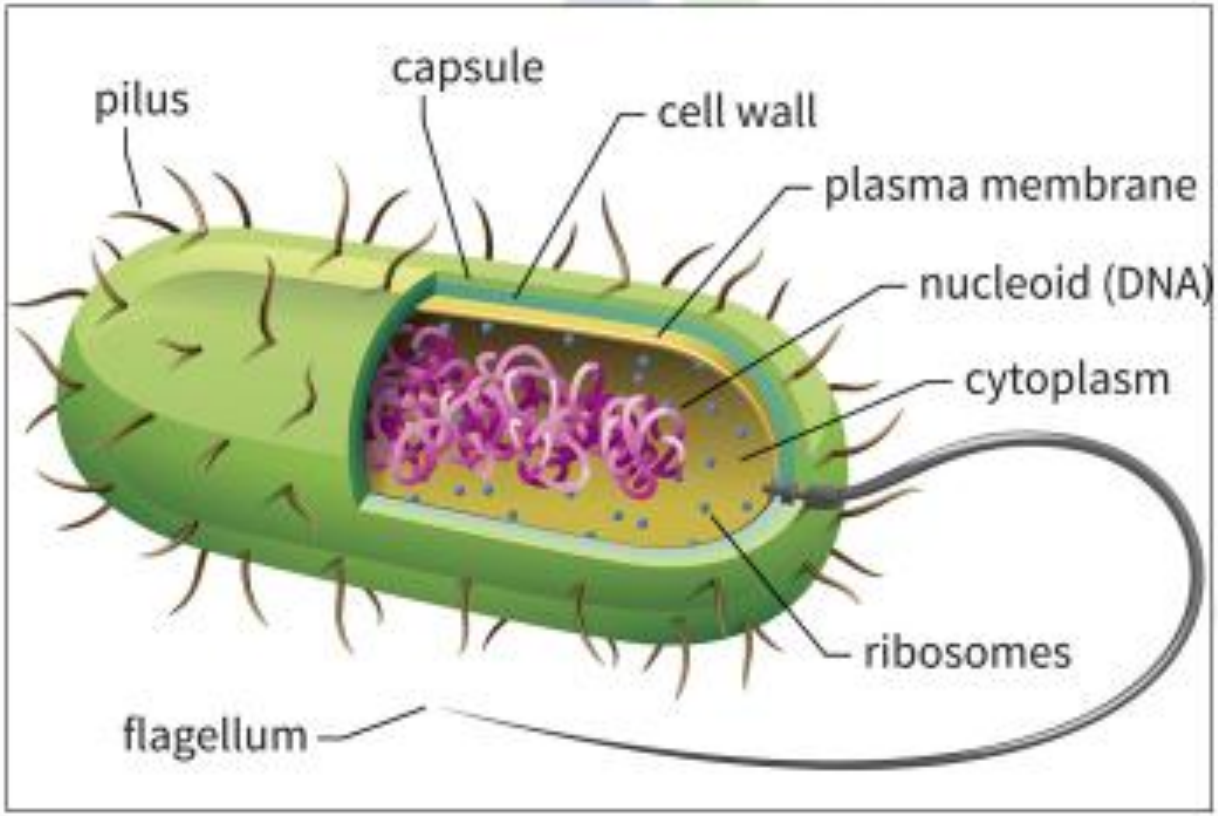


Cell-wall inhibitors:

General M.O.A:

They inhibit synthesis of cell wall → pores in cell wall → water enter the cell by **osmosity** → cell explosion → **Death of bacteria** !!

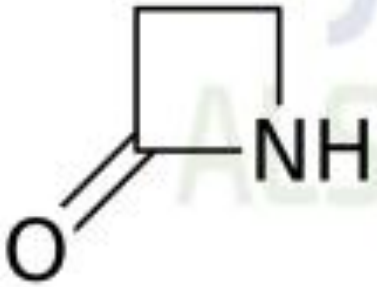
So, all of Cell-wall inhibitors are **bactericidals**.



Classification of Cell-wall inhibitors:

β-lactams

- Penicillins
- Cephalosporines
- Carbapenems
- Monobactams



Non β-lactams

- Vancomycin
- Fosfomysin
- Daptomycin
- Bacitracin
- Cycloserine

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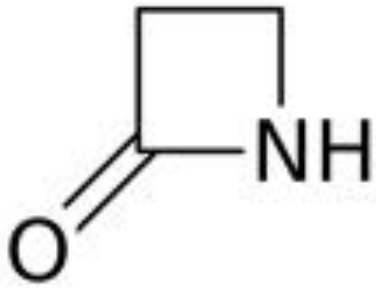
β-lactam الـحَـلـقـة الكيميائية



β-lactams الأدوية التي تحتوي على هذه الـحَـلـقـة

β-lactamase الإنزيم الذي يكسّر هذه الـحَـلـقـة

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Penicillins

Can be classified according to their **Spectrum** of activity into:

1) Narrow-spectrum penicillins.

2) Narrow-spectrum penicillins but resist β-lactamase enzymes.

3) Extended-spectrum penicillins.

4) Broad-spectrum penicillins:

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1) Narrow-spectrum penicillins

- **Narrow-spectrum**, act against types of (Gram +) bacteria only.

- **Main drugs:** **(Penicillin G – Penicillin V) :**

a) Penicillin G: is acid-labile, so used as injections only :

- **Benzyl** penicillin G

- **Benzathine** penicillin G (used for prophylaxis of rheumatic fever, syphilis).

- **Procaine** penicillin (procaine is a local anesthetic).

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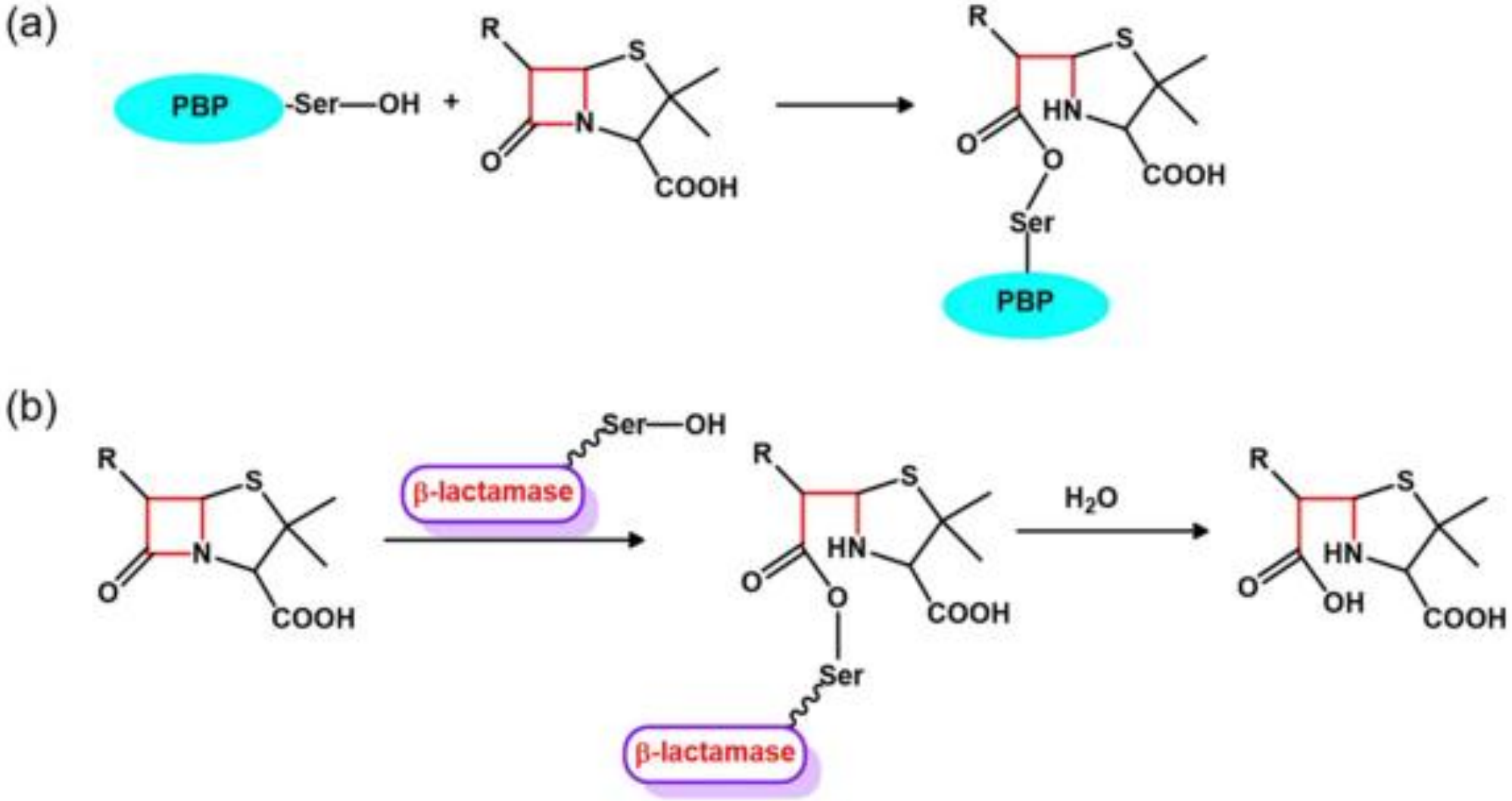
b) Penicillin V (Phenoxy-methyl-penicillin):

Is acid-stable, so can be used orally. But its absorption differs from one person to another, so we cannot use this drug in serious infections **(used for prophylaxis of rheumatic fever and for bacterial sore throat).**

- Bacteria can destroy Narrow-spectrum penicillins by secreting **β-lactamase (penicillinase)** enzymes !!



2) Narrow-spectrum penicillins but resist β-lactamase enzymes

(Anti - staphylococcal penicillins) :

- Narrow-spectrum, act against **staphylococcus** (Gram +) bacteria only, but these drugs **resist** many types of **β**-lactamase enzymes !!

- **Main drugs:**

a) Methicillin: withdrawn from market due to **Nephrotoxicity**.

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b) Cloxacillin and Flucloxacillin: are available in Yemen,

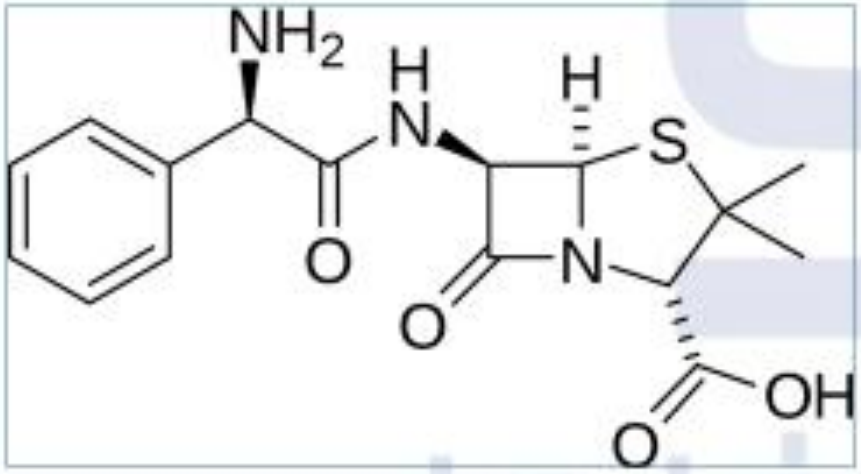
Flucloxacillin has better oral absorption and less GIT adverse effects.

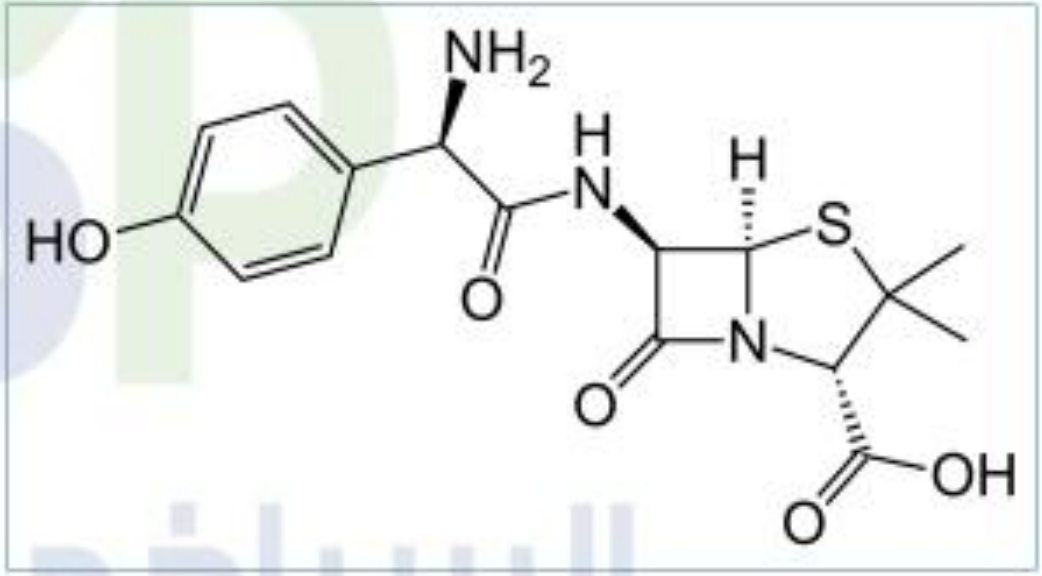
- **Main uses (usually as a combination):**

These drugs are mainly used to treat **staphylococcal** infections, e.g. **skin infections.**

3) Extended-spectrum penicillins:

a) Amino-penicillins: Ampicillin - Amoxicillin.





b) Anti-pseudomonal penicillins: Piperacillin (the most potent) - Ticarcillin.

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- Extended-spectrum, (Gram +) & some (Gram-) bacteria, but these drugs **don't resist** β-lactamase enzymes !!

- **Main uses:**

1) Amino-penicillins are mainly used for streptococcal infections, e.g.

Bacterial sore throat and in **prevention of infective endocarditis** (before dental procedures).

2) Amoxicillin is effective for H. pylori (in combination).

3) Ampicillin (with or without the addition of gentamicin) is the drug of choice for **Listeria monocytogenes**.

4) Piperacillin and Ticarcillin act against Pseudomonas aeruginosa (hospital-acquired infections).

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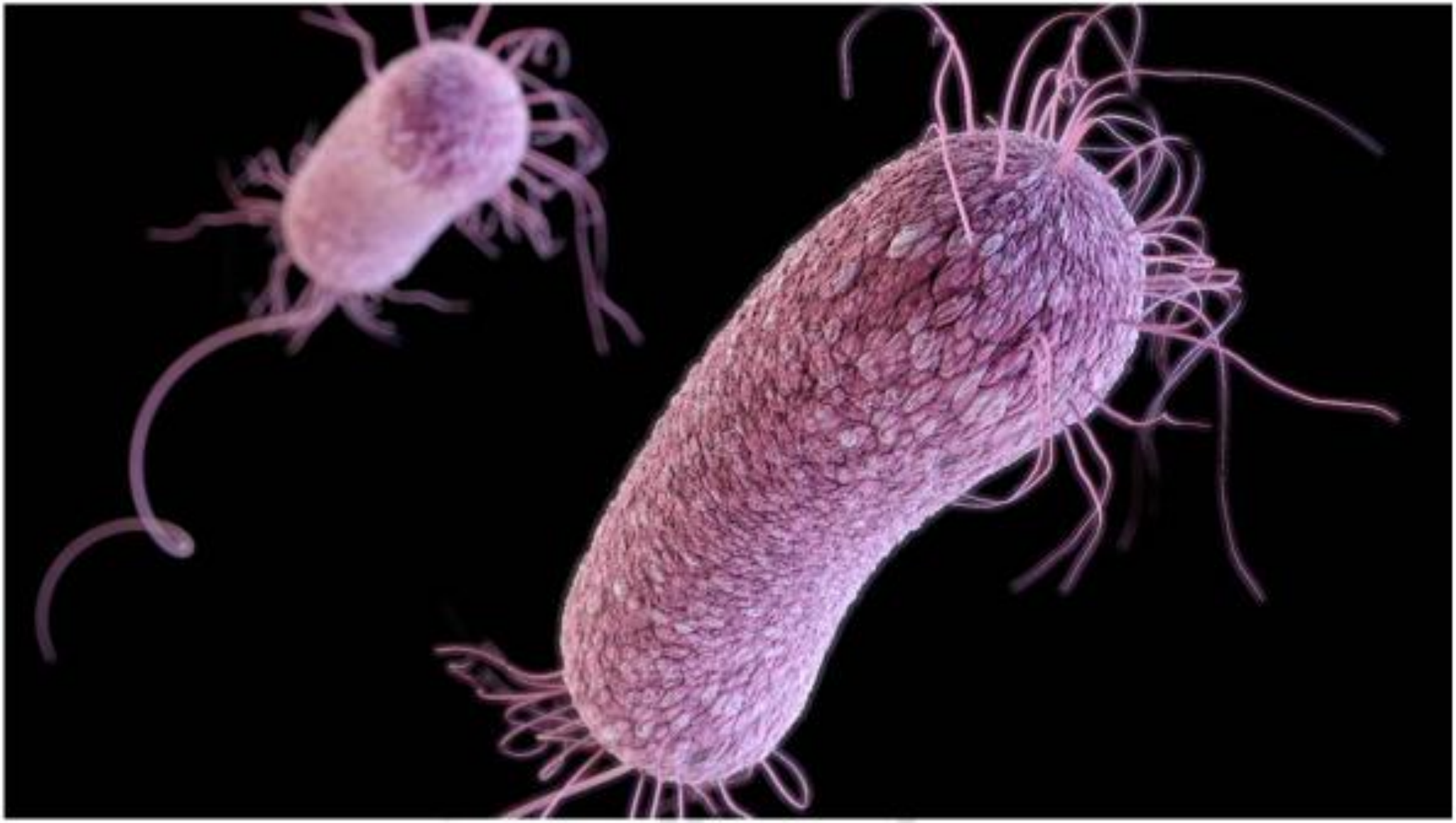

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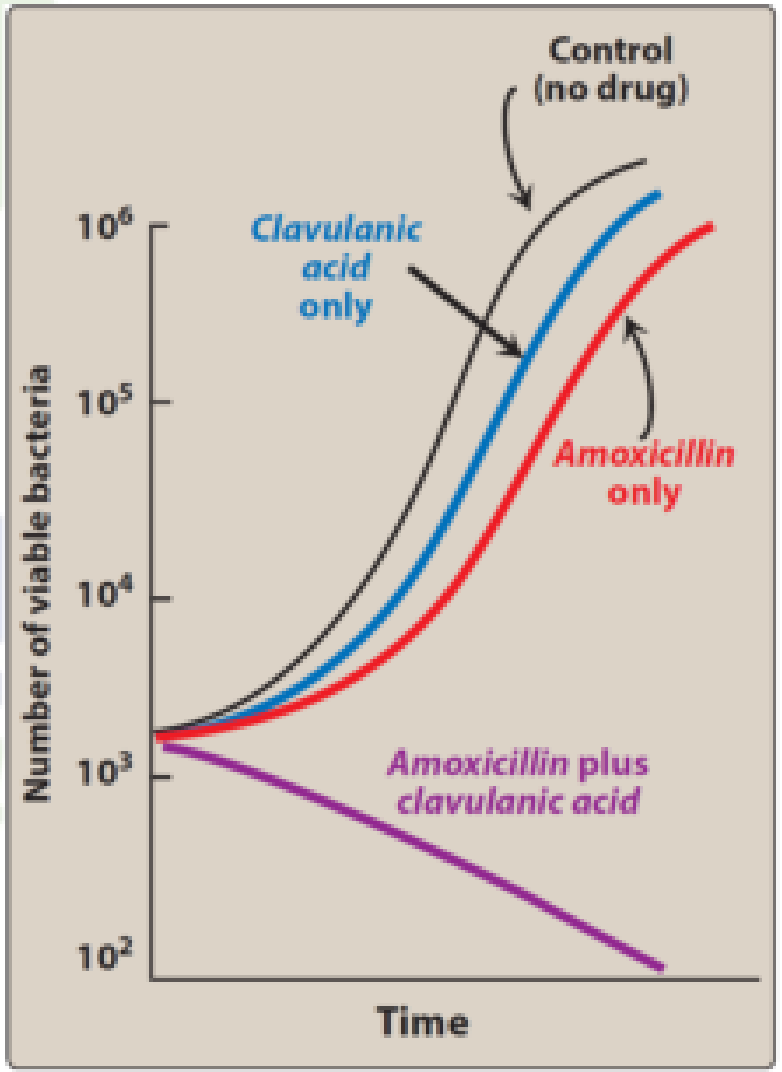
Pseudomonas aeruginosa

4) Broad-spectrum penicillins:

They are

(Extended-spectrum penicillin + β-lactamase inhibitor)

- Amoxicillin + clavulanate
- Ampicillin + sulbactam
- Piperacillin + tazobactam



- Extended-spectrum, (Gram +) & some (Gram-) bacteria, but these drugs **resist** many types of **β**-lactamase enzymes !!

Main uses:

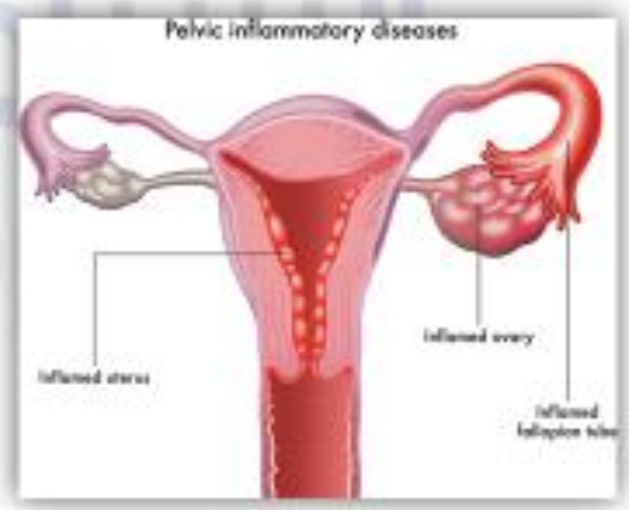
1) **Augmentin ®** is mainly used for **skin infections, respiratory infections, dental infections, bone and joint infections** and in certain types of **UTIs in pregnant women**.

2) Piperacillin + Tazobactam:

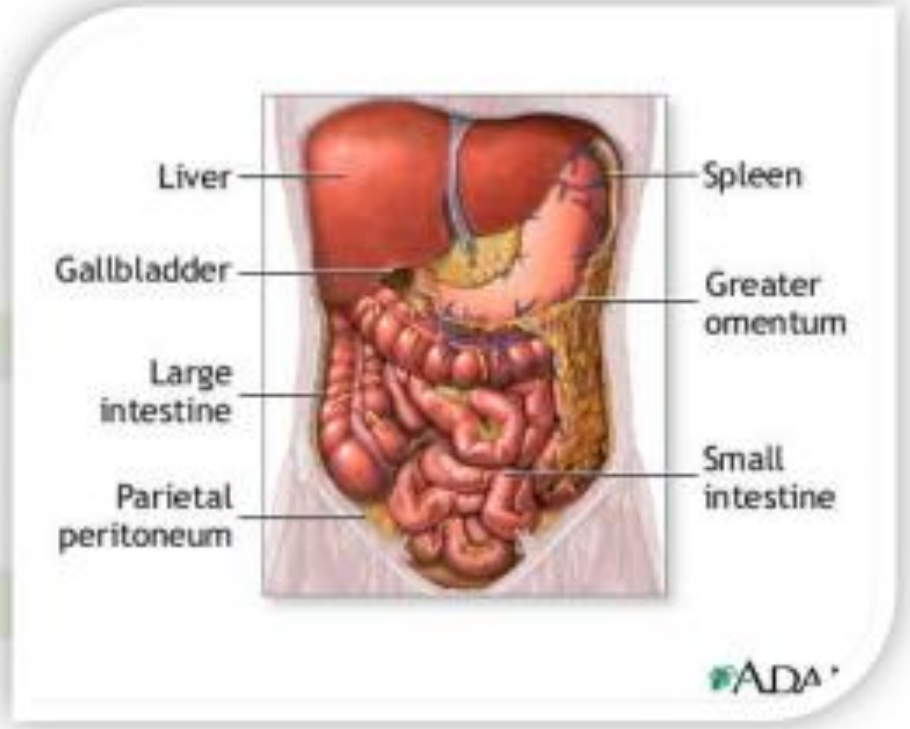
- Hospital-acquired infections (e.g. UTI, pneumonia, skin infection).
- Appendicitis (perforated)

IDSA
Infectious Diseases Society of America

- Diabetic foot.
- Pelvic inflammatory disease.



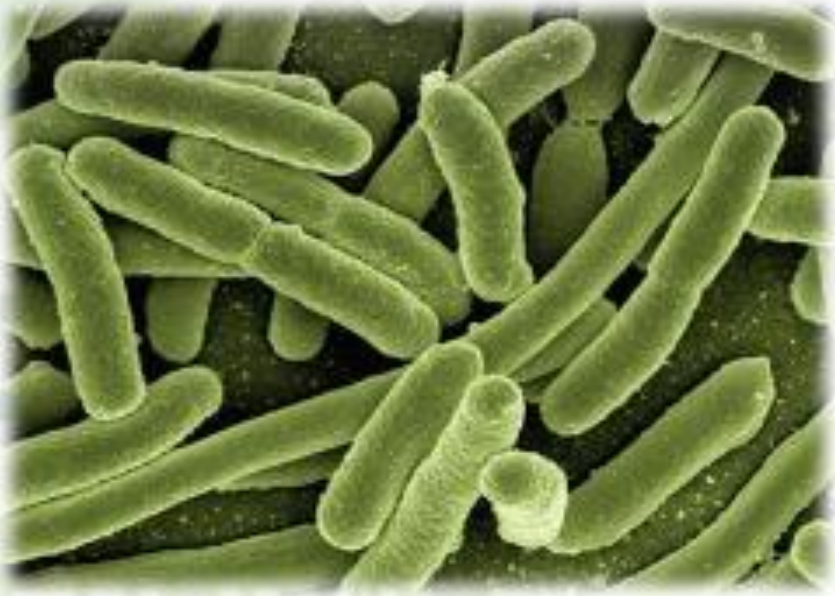
- **Intra-abdominal infections:**



- **Febrile neutropenia:**

General Adverse Effects of Penicillins

Selective Toxicity ??



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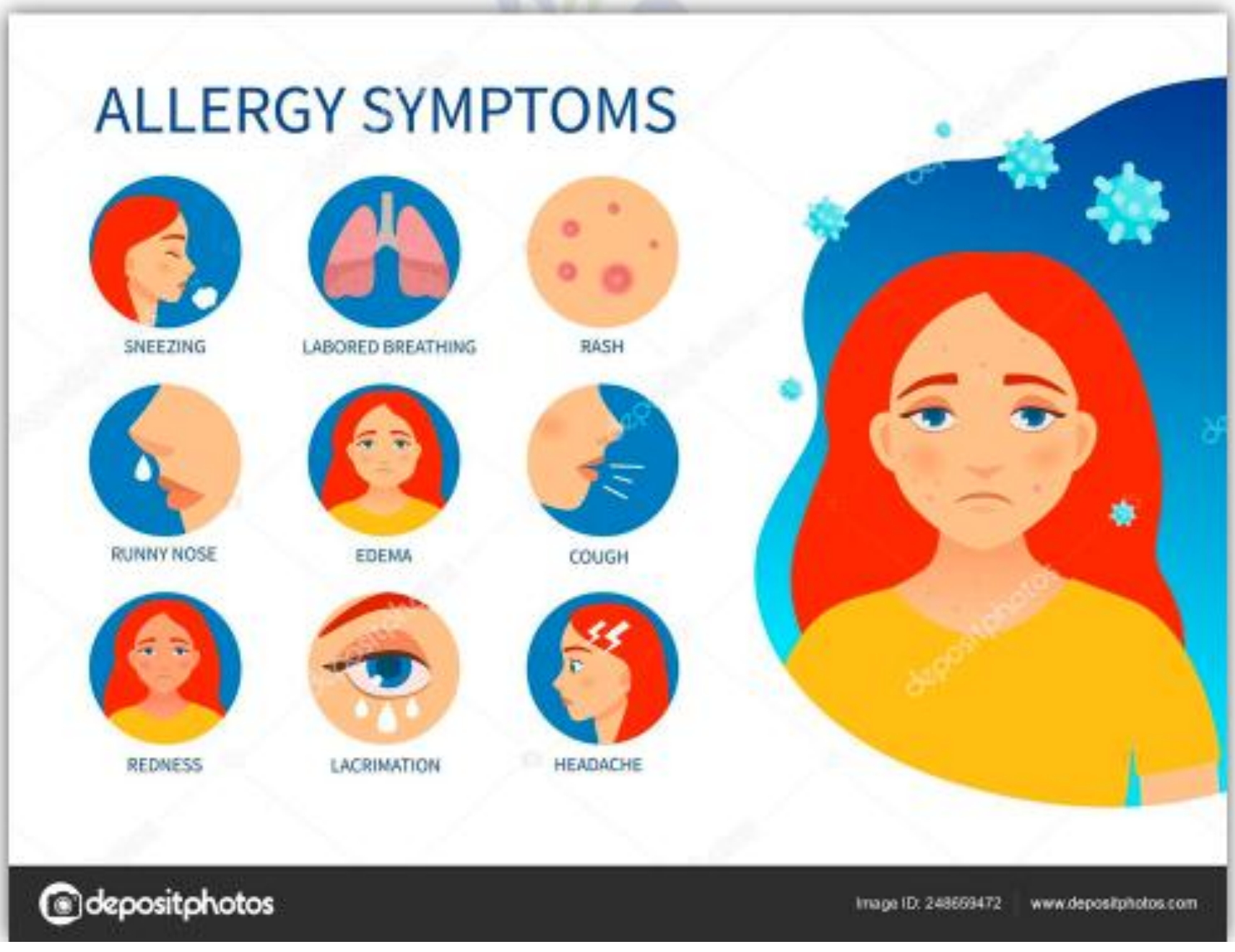
1) Hypersensitivity, may be severe or mild.



A) Severe allergy (Anaphylaxis):

Key signs of anaphylaxis:

- Marked upper airway (laryngeal) oedema and bronchospasm, causing stridor and wheezing
- Tachycardia (heart rate > 110 per minute) and increased respiratory rate

Symptoms include:

- Abdominal pain, vomiting, diarrhoea, and a sense of impending doom
- Flushing, but pallor might also occur
- Patients may also display symptoms of mild allergy (see Section 2.2)

Management:

- Assess the patient.
- Call for an ambulance.
- Secure the patient's airway and help to restore their blood pressure by laying the patient flat and raising their feet.
- Remove the source of anaphylaxis, if known, using suction if required.

Oxygen 100% 15 L/min (for adults or children).

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Adrenaline (epinephrine) 1mg/ml, one dose **IM**, to be repeated every 5 min if needed (until the specialist critical care is available):

Birth – 6 months: 0.10 ml

6 months - 6 years: 0.15 ml

6 years - 18 years:

weight < 30 kg: 0.30 ml

weight ≥ 30 kg: 0.50 ml

Adults: 0.50 ml

IM Adrenaline (for anaphylaxis) is preferred to be injected in the anterolateral aspect of the middle third of the thigh.

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B) Mild Allergy:

Key signs of mild allergy:

- Urticaria and rash, particularly of chest, hands and feet
- Rhinitis, conjunctivitis

- Mild bronchospasm without evidence of severe shortness of breath

Management:

A) Anti-histamine:

Loratadine

فموياً (للأطفال من عمر سنة فما فوق) قبل الطعام أو معه أو بعده، لعلاج الحساسية والحكة:

أقل من سنة: لا توجد معلومات (حتى الآن).

سنة - سنتين: 2.5 مجم مرة واحدة يومياً .

سنتين - 12 سنة:

وزن الطفل ≥ 30 كجم: 5 مجم مرة واحدة يومياً .

وزن الطفل أكثر من 30 كجم: 10 مجم مرة واحدة يومياً .

12 سنة فما فوق والبالغون: 10 مجم مرة واحدة يومياً .

في كبار السن (ما دام الكبد والكلى سليمين): يمكن استعماله بنفس جرعة البالغين .

Chlorpheniramine (chlorphenamine)

فموياً (للأطفال من عمر شهر فما فوق) قبل الطعام أو معه أو بعده، لعلاج الحساسية والحكة:

أقل من شهر: **ممنوع !!**
شهر - سنتين: **1** مجم **مرتين** يومياً .
سنتين- 6 سنوات: **1** مجم كل **4-6 ساعات** (بشرط أن لا يزيد عدد الجرعات عن **6 جرعات** يومياً).
6 سنوات - 12 سنة: **2** مجم كل **4-6 ساعات** (بشرط أن لا يزيد عدد الجرعات عن **6 جرعات** يومياً).
12 سنة فما فوق والبالغون: **4** مجم كل **4-6 ساعات** (بشرط أن لا يزيد عدد الجرعات عن **6 جرعات** يومياً).

في كبار السن (ما دام الكبد والكلى سليمين): يفضّل استعمال أدوية الجيل الثاني ما دامت فعالة في علاج نفس المرض .. وإذا استعملنا هذا الدواء فإن جرعته تصبح **4** مجم **كل 12-24 ساعة** (مع مراعاة التأثيرات المحتملة لهذا الدواء على سرعة القلب وتضخم البروستات والمياه الزرقاء والإمساك والقدرة على التفكير).

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2) GIT upset (nausea, vomiting):

- If the drug is given oral → use with food (if possible) or with a lot of water.
- If drug is given as an injection → give **ondansetron** or **metoclopramide**.

3) Antibiotic-associated diarrhea and pseudo-membranous colitis:

Due to death of normal flora → ↑ activity of Cl. difficile bacteria → infection.

Diagnosis: by one the following tests:

1) Testing the presence of **toxins A + B** by enzyme immunoassay (EIA).

2) Testing the presence of the gene that produces toxin B using "Polymerase Chain Reaction" **(PCR)** test.

Treatment:

- Usually without admission to hospital, by **oral/IV metronidazole** (500 mg, three times daily, for 10-14 days) ⟹ if no improvement after 5 days, give **oral vancomycin (or oral fidaxomicin)**.

- Rehydration (ORS or IV).

- Do **NOT** use an anti-spasmodic or diarrhea-stopping drug (e.g. Loperamide).

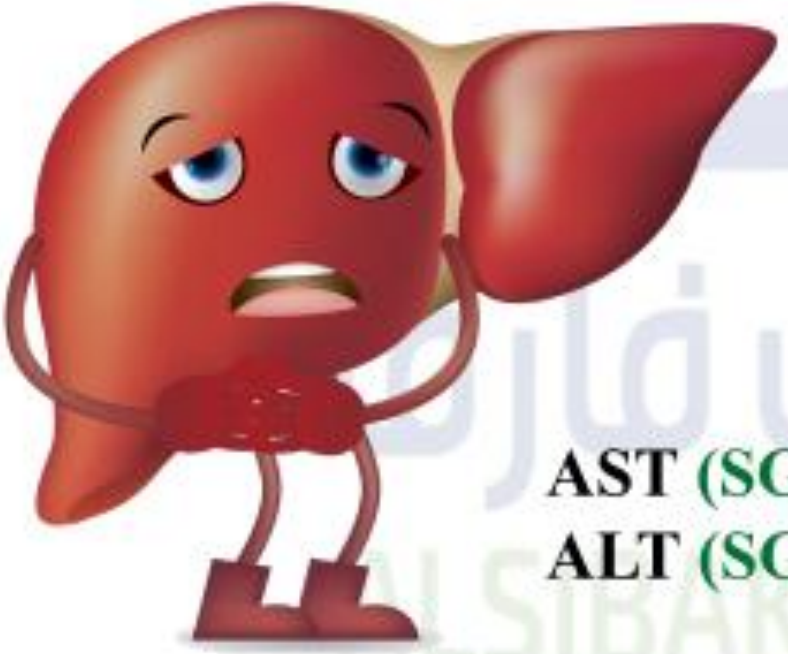
4) Neuro-toxicity: penicillins are irritating to neuronal tissue → may cause **seizures** if injected intrathecally or if very high blood levels are reached (e.g. patients of renal failure).

5) Nephro-toxicity:

- Penicillins are generally not nephrotoxic (except methicillin that has been withdrawn from the market).

6) Hepato-toxicity:

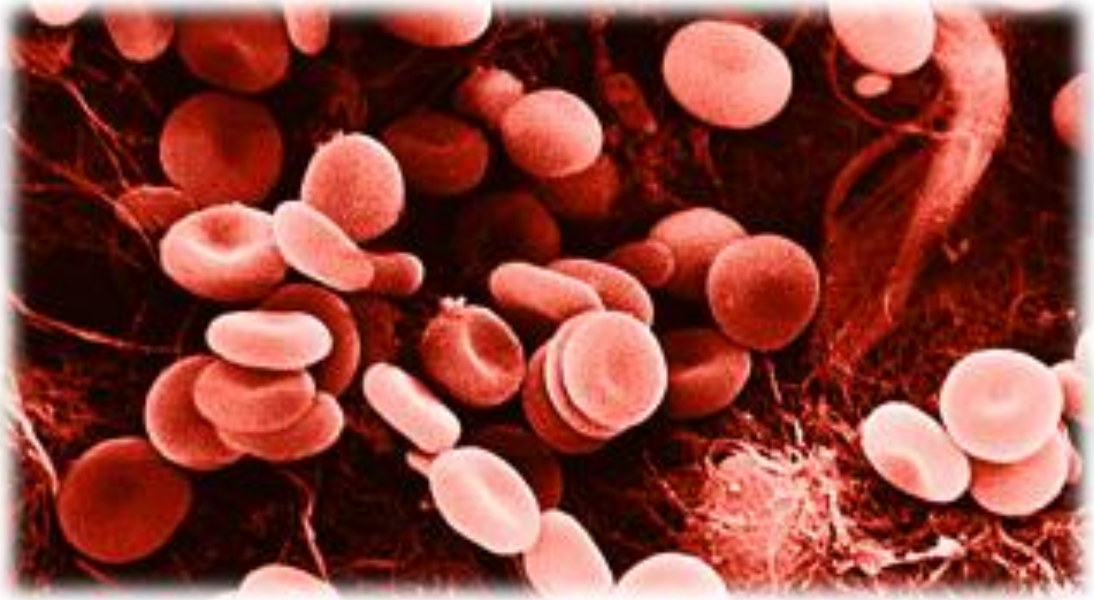
Clavulanic acid may be hepato-toxic → monitor liver functions if treatment continues > 14 days.



AST (SGOT)
ALT (SGPT)

7) Hematologic toxicities:

- **Decreased coagulation** may be observed with high doses of piperacillin → monitor INR.
- **Cytopenias** have been associated with therapy of **more than 2 weeks** → monitor CBC every week.

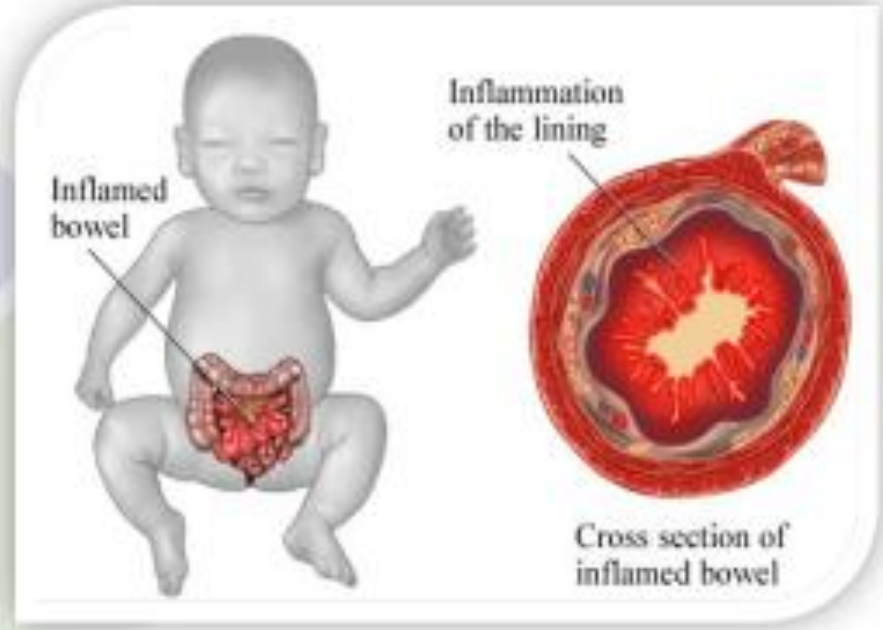


Penicillins & Pregnancy

The following drugs can be used during pregnancy (according to **animal** studies and/or **human** data):

- Benzyl penicillin G - Benzathine penicillin G (with or without lidocaine) - Procaine penicillin G - Penicillin V.

- Cloxacillin - Flucloxacillin -Ampicillin -Amoxicillin.



- Amoxicillin & clavulanate **(Augmentin)** can be used, but it may ↑ the risk of **neonatal necrotizing enterocolitis** if used in the "premature rupture of membranes" (unconfirmed Australian & Swedish studies).

Penicillins & Breastfeeding:

- Benzyl penicillin G - Benzathine penicillin G (with or without lidocaine) - Procaine penicillin G - Penicillin V.
- Cloxacillin - Flucloxacillin -Ampicillin -Amoxicillin.
- Amoxicillin & clavulanate - Piperacillin & Tazobactam - Ticarcillin & Clavulanate.

Penicillins & Food

All oral penicillins should be used on an **empty stomach** (1 hour before food or 2 hours after it), Except:

- **Amoxicillin** can be used without regard to food.
- **Amoxicillin & Clavulanate** should be used on a full stomach.
- **Penicillin V** is **preferred** to be used on an empty stomach, but may be used on a full stomach

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Cephalosporines

First Generation:

- Narrow-spectrum, act mainly against (Gram +) bacteria, but these drugs **resist** many types of **β**-lactamase enzymes

- **Main drugs:** **Cephalexin, Cephradine, Cefadroxil** and **Cefazolin.**

- **Main uses:**

1) Used for G+ bacterial infections, e.g. **skin infections** and **bacterial sore throat**.

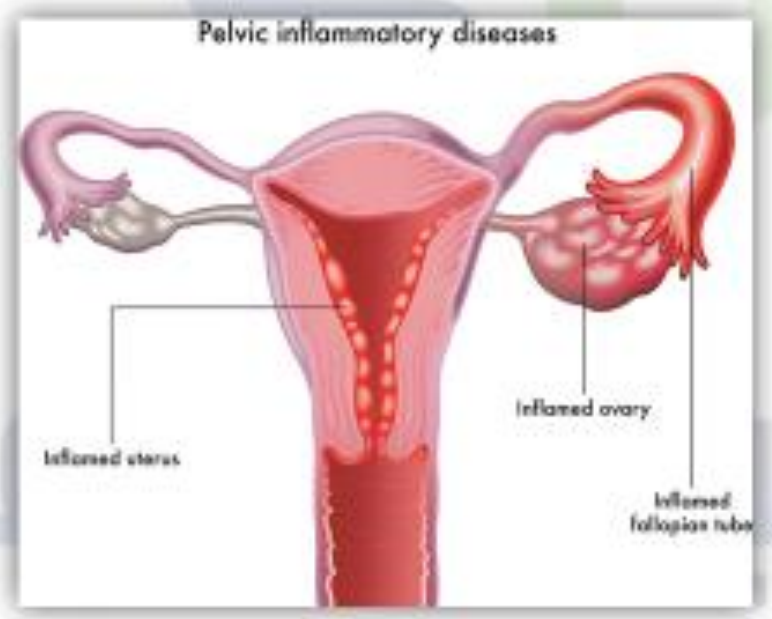
2) Cefazolin is commonly used for **surgical prophylaxis.**

Second Generation:

- Extended-spectrum, act against types of (Gram + and -) bacteria. They are less potent against (Gram+) bacteria than the 1st generation.
- Cefuroxime **resists** many types of **β**-lactamase enzymes !!
- Cefoxitin and Cefotetan are effective against types of anaerobic bacteria.
- **Main drugs:** **Cefuroxime , Cefaclor, Cefoxitin, Cefotetan** and **Cefprozil.**

•Main uses:

1) RTIs : e.g. bacterial sore throat, sinusitis, otitis media.
2) **Cefuroxime** can be used for skin infections. Also for UTIs in pregnant women, and for meningitis.



3) Cefoxitin and Cefotetan can be used for peritonitis and pelvic inflammatory disease (anaerobic bacteria) !!

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Third Generation:

- Broad-spectrum, act against types of (Gram + and -) bacteria. They are less potent against (Gram+) bacteria than 2nd generation, but they have more activity against (Gram-) bacteria.

- Cefdinir **resists** many types of **β**-lactamase enzymes !!

Main drugs: **Ceftriaxone, cefotaxime, ceftazidim, cefoperazone, cefixim, cefdinir** and **cefpodoxime**

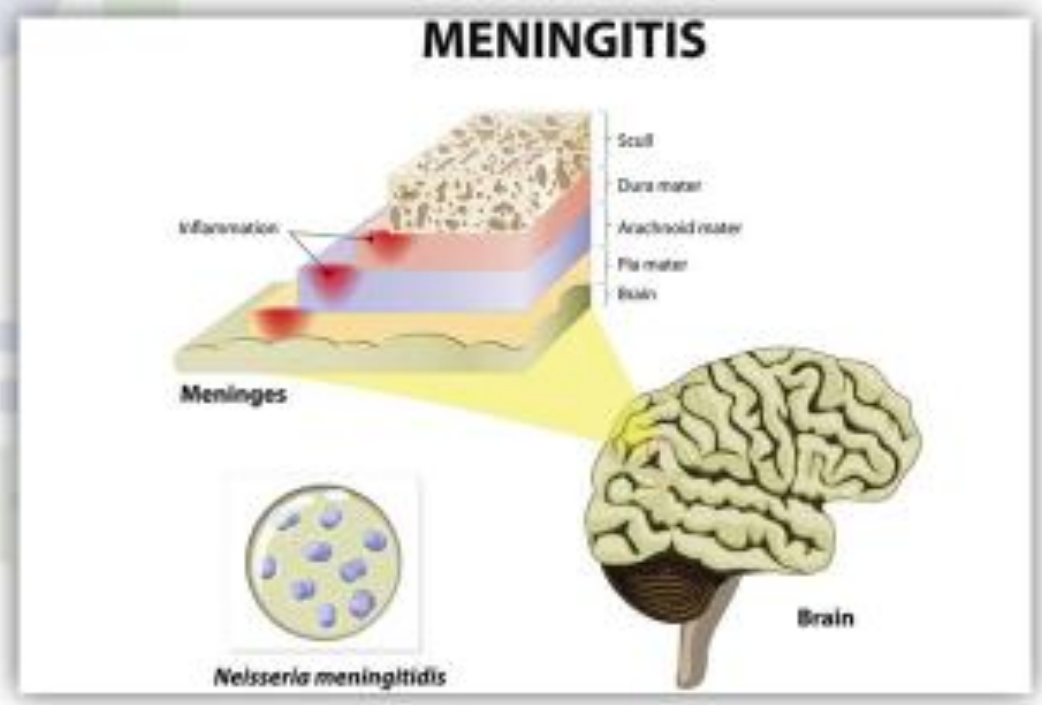
- **Main uses:**

1) RTIs : e.g. bacterial sore throat, sinusitis, otitis media, pneumonia.

2) UTIs, e.g. in pregnant women.

3) Ceftriaxone and cefotaxime pass meninges well, so they are **DOCs for meningitis**.

They are also the DOCs for **"typhoid fever"**



Fourth Generation:

Broad-spectrum, act against types of (Gram + and -) bacteria, but has more activity against (Gram -) bacteria

- Cefepim **resists** many types of **β**-lactamase enzymes !!
- Cefepim is active against Pseudomonas aeruginosa.

- **Main drugs:** **Cefipim** (Also **Cefpirome** in some countries).

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• Main uses:

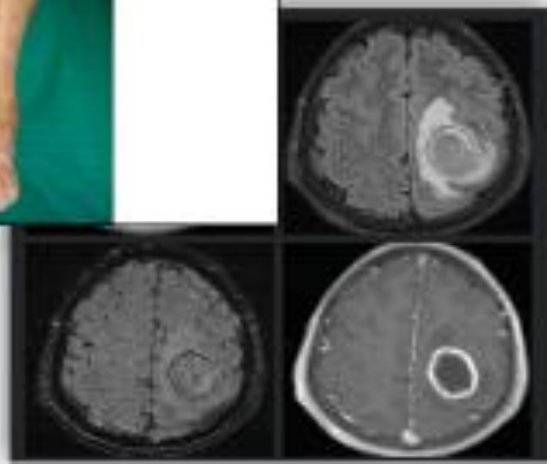
1) Nosocomial infections (Pneumonia, skin infections, UTIs).

2) Febrile neutropenia (controversial, but the FDA's analyses does not confirm any ↑ in mortality).

3) Intra-abdominal infections.

4) Diabetic foot (preferred in the warm climate, IDSA).

4) Brain abscess.



5) Meningitis (especially if hospital-acquired or in immuno-compromised patients).

Fifth Generation:

- Broad-spectrum, act against types of (Gram + and -) bacteria. Very effective against Gram + bacteria, including MRSA and VRSA.

MRSA= Methicillin-resistant Staphylococcus aureus.

VRSA= Vancomycin-resistant Staphylococcus aureus.

- **Main drugs:** **Ceftaroline** and **Ceftobiprole.**

- **Main uses:**

1) Pneumonia, skin infections.
2) Bacteremia, endocarditis, and osteomyelitis.

Cross hypersensitivity between penicillins and cephalosporines:

• Cross-hypersensitivity with penicillins may occur, especially the 1st generation cephalosporins.

Cephalosporines that have the least cross-hypersensitivity with penicillins are:

- **BNF: Cefuroxime, ceftriaxone, cefotaxime, cefixime, ceftazidime.**
- **AAP: Cefuroxime, cefdinir, cefpodoxime.**

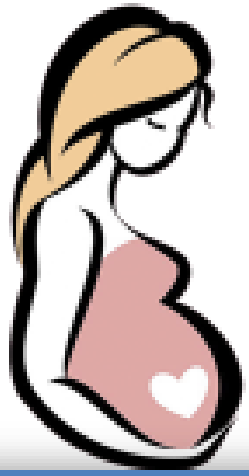
Nephro-toxicity of Cephalosporines:

- **Cephalosporines** may be nephrotoxic if used in the maximum dose or for more than 10 days (monitor serum creatinine or cystatin C).

Serum creatinine

Cystatin C

Cephalosporines & Pregnancy

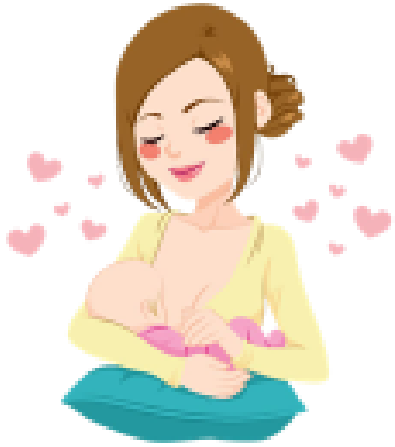


The following drugs can be used during pregnancy (according to **animal** studies and/or **human** data):

- **1st generation:** Cephalexin (Cefalexin) - Cefadroxil - Cefazolin - Cephradine (Cefradine).

- **2nd generation:** Cefuroxime-Cefaclor-Cefotetan-Cefoxitin.
- **3rd generation:** Ceftriaxone - Cefotaxime - Cefixime - Ceftazidime - Cefpodoxime.
- **4th generation:** Cefepime.
- **5th generation:** Ceftaroline.

Cephalosporins & Breastfeeding:



- **1st generation:** Cephalexin (Cefalexin) - Cefadroxil - Cefazolin - Cephradine (Cefradine).
- **2nd generation:** Cefuroxime - Cefaclor - Cefotetan - Cefoxitin - Cefprozil.
- **3rd generation:** Ceftriaxone - Cefotaxime - Cefixime - Ceftazidime - Cefpodoxime.
- **4th generation:** Ceftriaxone - Cefotaxime - Cefixime - Ceftazidime - Cefpodoxime.

Cephalosporines & Food

All of oral cephalosporines can be used **without regard to food**, except:

- **Cefuroxime axetil** should be used on a full stomach (food ↑ bioavailability from 37% to 52%).

- **Cefpodoxime** should be used on a full stomach.

NOTES:

1) Cefpodoxime should be separated by 2 hours from antacids.

2) Cefdinir should be separated by 2 hours from Mg^{2+} and Al^{3+} salts.

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Carbapenems:

- **Main drugs:** **Imipenem**, **meropenem**, **doripenem** and **ertapenem**.

- Broad-spectrum, act against many types of (Gram + and -) and anaerobic bacteria. They resist most types of **β**-lactamase enzymes. All of them, except ertapenem, are effective against Pseudomonas aeruginosa.

- **Imipenem** is compounded with **cilastatin** to protect it from metabolism by renal dehydropeptidase → ↑activity and ↓ nephro-toxicity of imipenem.

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- **Main uses:**

1) Empirical therapy for serious infections, e.g. febrile neutropenia and diabetic foot.

2) Complicated skin infections, complicated UTIs.

- **Adverse effects:**

1) Hypersensitivity (cross hypersensitivity with penicillins is less than 1%).

2) Antibiotic-associated diarrhea, nausea and vomiting.

3) High levels of **imipenem**, especially in patients with renal failure, may cause seizures (the other carbapenems are much less likely to do that).

- **Meropenem** is the safest carbapenem for **pregnant** women.
- In **breastfeeding** women, use Imipenem/cilastain or meropenem.

Monobactams:

- **Main drugs: Aztreonam.**

- Narrow-spectrum, act against many types of (Gram -) bacteria, including Pseudomonas aeruginosa. It resists most types of β-lactamase enzymes.

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- **Adverse effects:**

1) Hypersensitivity (little cross hypersensitivity with the other β-lactam antibiotics).

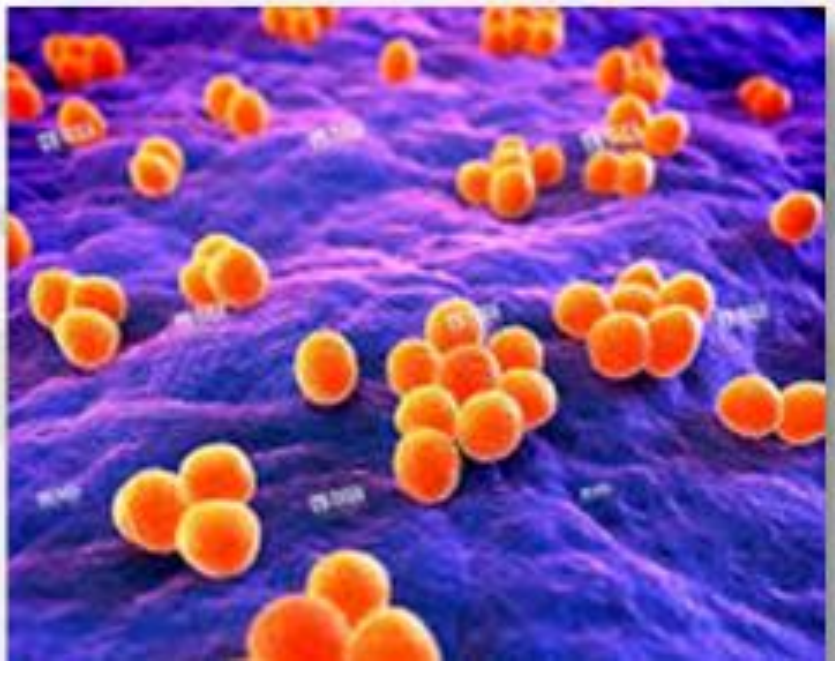
2) Thrombo-phlebitis (at the site of injection).

Aztreonam can be used in pregnant and breastfeeding women.

Non- β-lactam Cell-wall inhibitors:

1) Vancomycin:

- Narrow-spectrum, very effective against of (Gram +) bacteria, including MRSA.
- Has high molecular weight, so can't penetrate cell membrane of (Gram -) bacteria.



- **Main uses:**

1) **IV Vancomycin:** MRSA infections (skin - endocarditis - septicemia).

2) **Oral Vancomycin:** Poorly absorbed, used for antibiotic-associated diarrhea due to Clostridium diffcile bacteria.

Adverse effects:

1) Oral Vancomycin: nausea, vomiting, flatulence and nephrotoxicity (rare).

Use with food.

2) IV Vancomycin:

- **A) Nephrotoxicity:**

Monitor its serum conc. just before the 4th dose (steady state is usually achieved), then every week → should be 10-15 mg/L (15-20 mg/L in severe infections).

+ monitor serum creatinine or cystatin C.

b) Red-man syndrome (because of the rapid infusion).

Prophylaxis (by slow IV infusion):

1) Reconstitute each 500-mg vial with 10mL distilled water.
2) Each 500 mg must be added to a minimum of 100mL of NS 0.9% or Gluc 5%.

3) The solution should be clear and colorless.

4) Give by IV infusion (containing 500 mg) over a minimum of 1 hour, to reduce the risk of 'red man' syndrome, hypotension and thrombo-phlebitis.

Treatment of Red Man Syndrome:

1) Stop the vancomycin infusion immediately.
2) Give Diphenhydramine 50 mg IV (over 2 minutes).

3) Give Famotidine 20 mg IV (add 3-8 ml of NS, and administer over 2 minutes).

4) Re-infuse vancomycin over the right rate (or slower if needed).

c) Ototoxicity:

- Toxicity on hair cells → Deafness.
- Toxicity on vestibule → Vertigo.

2) Fosfomycin:

- Narrow-spectrum, effective against some of (Gram -) bacteria, especially E. coli.
- Well-distributed in urinary tract and prostate.

- **Main uses:**

1) **UTIs:** that caused by E. coli (uncomplicated cystitis in women).

2) **Prostatitis**

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Adverse effects:

Diarrhea, nausea, vaginitis, and headache.

- **Fosfomycin** can be used in pregnant & breastfeeding women (as a single oral dose).
- Powder should be dissolved in 90-120 ml of water **(neither hot, nor cold),** and taken on an empty stomach.

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3) Daptomycin:

- Narrow-spectrum, effective against some of (Gram +) bacteria, including MRSA and VRE.
- Daptomycin is inactivated by pulmonary surfactants → **NEVER** used in the treatment of pneumonia.

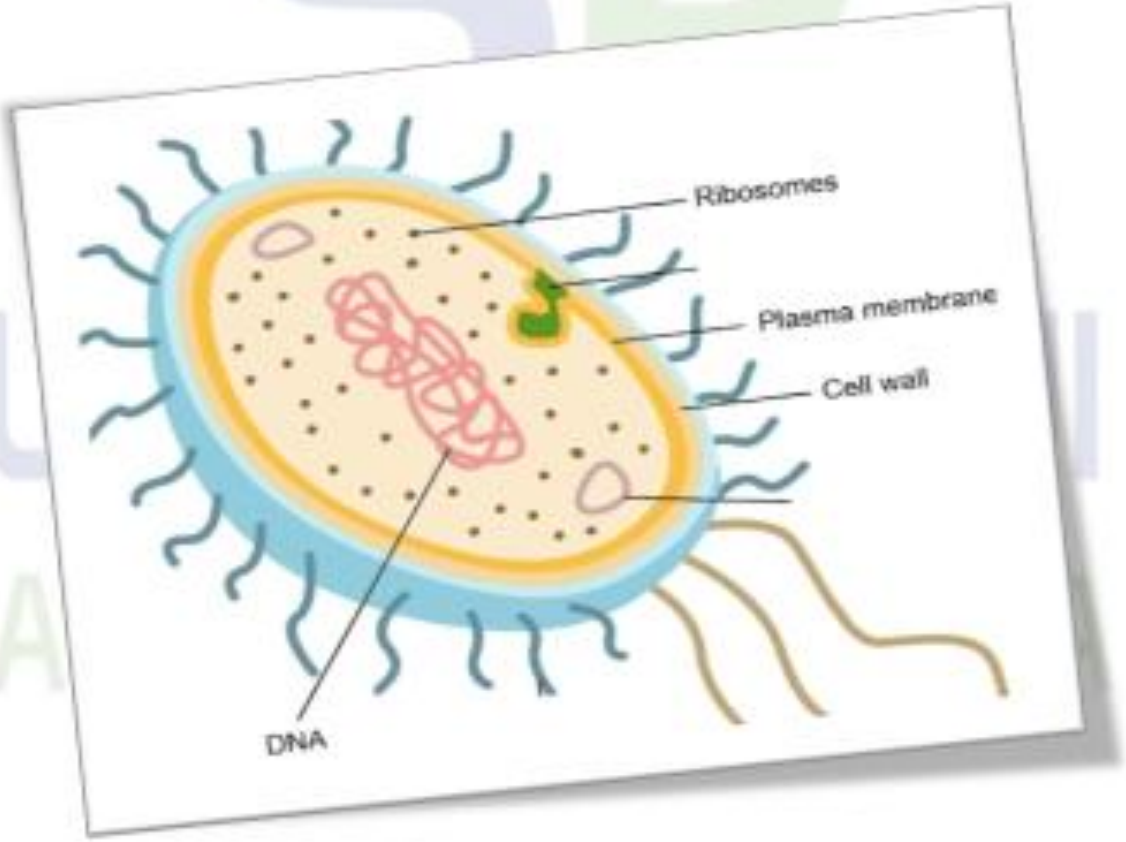
4) Bacitracin:

- Narrow-spectrum, effective against normal flora of skin (Gram+ bacteria).
- Very nephrotoxic (used topically only).

5) Cycloserine:

Used as second line in treatment of T.B.

2) Cell Membrane disrupters (Polymyxins) :



- Narrow-spectrum, effective against some of (Gram-) bacteria.

i) Polymyxin B: used topically, for skin, eyes or ears.

ii) Polymyxin E (Colistin):

available as a prodrug, **Colistimethate sodium**, which is administered IV or inhaled by a nebulizer.

Adverse effects:

With systemic use: nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness).

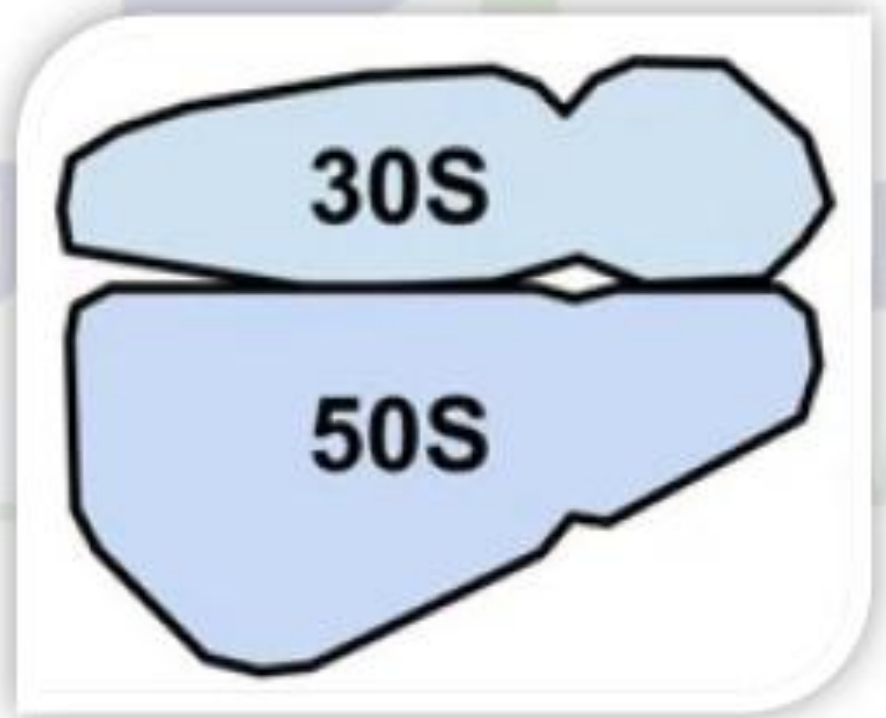
NDC 61314-628-10
Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution, USP
℞ only
STERILE
10 mL
SANDOZ

1 Vial
NDC 39822-0615-1
Colistimethate for Injection USP
LATEX FREE STOPPER
Equivalent to 150 mg* colistin
FOR INTRAMUSCULAR AND INTRAVENOUS USE
℞ only
XGEN

3) Protein-synthesis Inhibitors:

30S inhibitors

50S inhibitors



30S inhibitors

Amino-glycosides:

Streptomycin.

Gentamicin.

Amikacin.

Tobramycin.

Neomycin

Tetracyclines:

Tetracycline.

Doxycycline.

Minocycline

Demeclocycline.

Tigecycline*

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50S inhibitors

Macrolides:

Erythromycin.

Clarithromycin.

Azithromycin.

Roxithromycin.

Spiramycin.

Telithromycin*

Linosamides:

Lincomycin.

Clindamycin.

Others:

Chloramphenicol.

Linezolid.

Quinupristin/Dalfopristin

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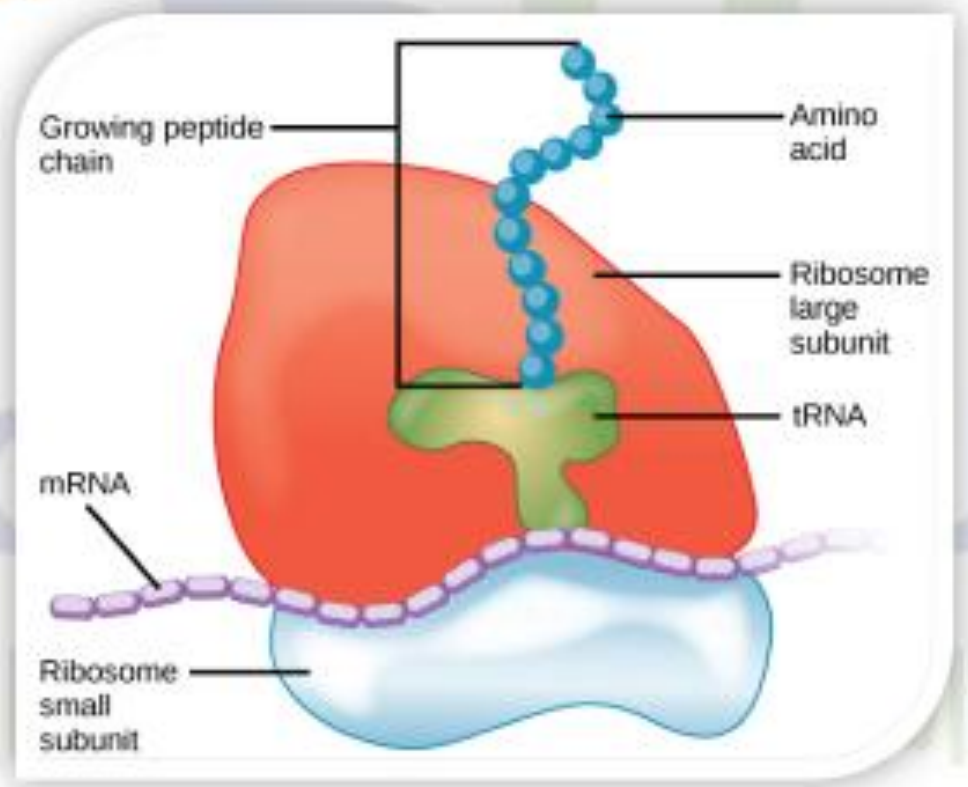
General M.O.A:

- **Protein-synthesis inhibitors** inhibit (30S or 50S) bacterial **ribosome** → inhibit synthesis of protein → bacteria will not have the essential proteins for growth and devision → **Bacteriostatics**.



Aminoglycosides also produce toxic proteins → **Bactericidals**.

Aminoglycosides

- **<u>Main drugs:</u> Streptomycin - Gentamicin - Amikacin - Tobramycin - Neomycin.**

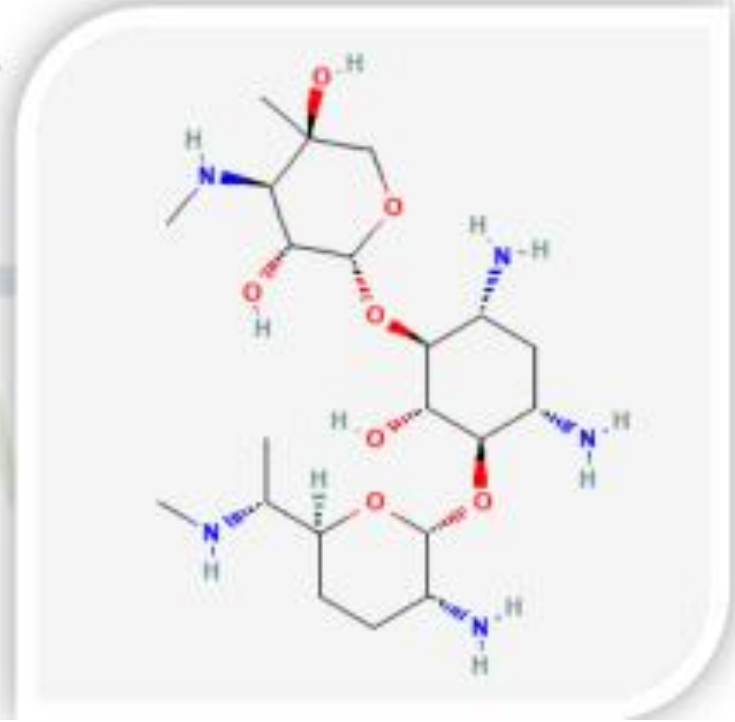
- Narrow-spectrum, act mainly against (Gram -) bacteria. Gentamicin acts also against many types of (Gram+) bacteria.

They act only against **<u>aerobic</u>** bacteria, because they need **Oxygen** to pass cell membrane.

Pharmacokinetics notes:

- **Absorption:** Aminoglycosides are very polar drugs → poorly absorbed by GIT → used systemically as injections only.

- **Distribution:** Low distribution into fatty tissue → aminoglycosides dose is calculated based on lean body mass(not actual body weight).



Main uses:

Used **systemically** to treat infections due to (aerobic gram-) bacteria, e.g:

1) In combination with other drugs in empiric therapy, e.g. diabetic foot, pneumonia.

2) UTIs.

- **Amikacin** is **less affected** by "specific enzymes" secreted by bacteria to resist aminoglycosides.

Oral neomycin has poor bioavailability (3%) & used for:

- Pre-operative **intestinal anti-sepsis.**
- **Hepatic encephalopathy** (acute or chronic).

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Main adverse effects:

1) Oto-toxicity:

- Toxicity on vestibule → Vertigo.
- Toxicity on hair cells → Deafness.

2) Nephro-toxicity (may be decreased by accurate doses).

3) Neuromuscular paralysis: may occur by:

- High serum conc., e.g. rapid IV infusion.
- If injected intra-pleurally.

Treated immediately by parenteral **calcium gluconate** or **neostigmine**.

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4) Allergy: especially dermatitis due to topical **neomycin**.

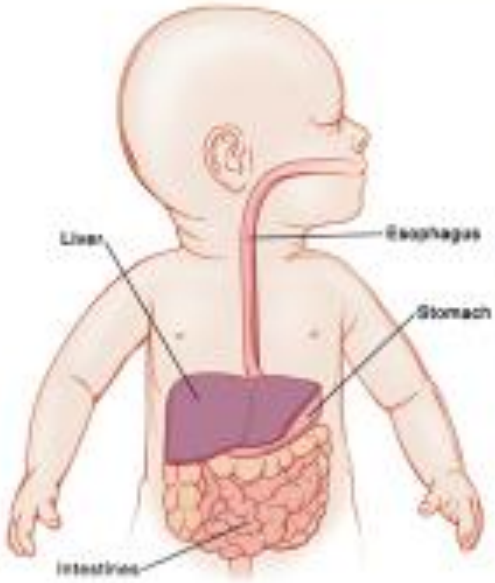
Aminoglycosides & Pregnancy

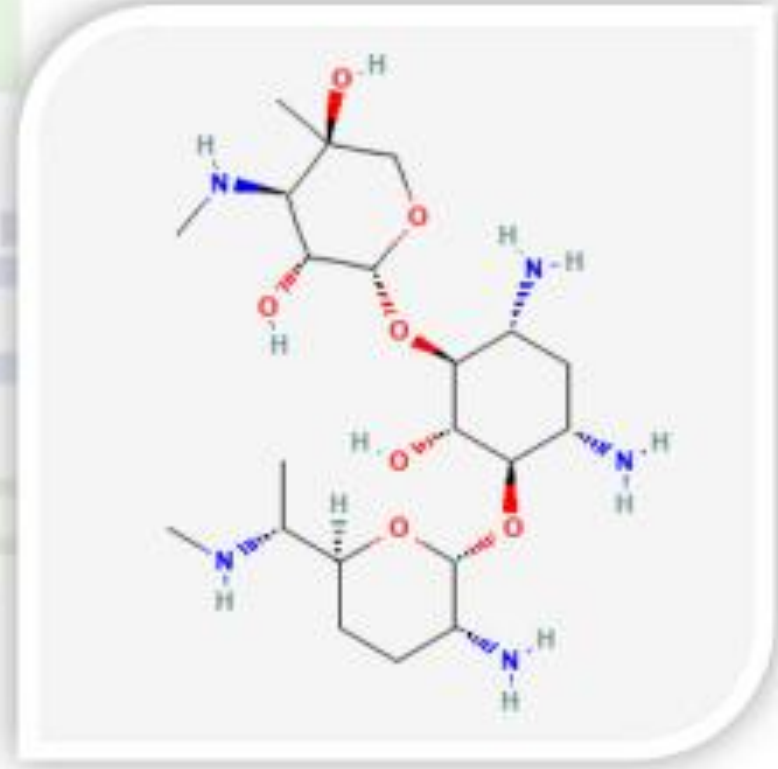
- Aminoglycosides should be avoided due to risk of fetal **ototoxicity** and **nephrotoxicity** **(except ophthalmic tobramycin).**

- When systemic aminoglycosides are absolutely necessary, **gentamicin** is preferred (then tobramycin).

Aminoglycosides & Breastfeeding:

Aminoglycosides can be used because they have poor oral absorption. However, **Streptomycin** and **gentamicin** are preferred (more clinical trials).

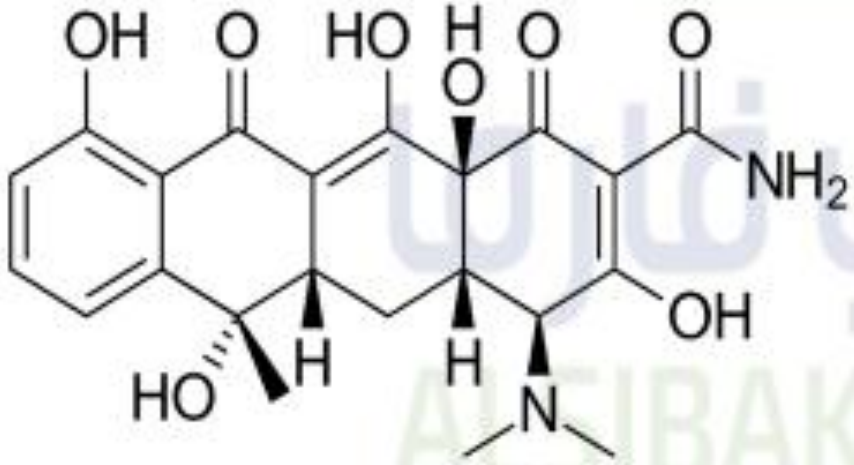


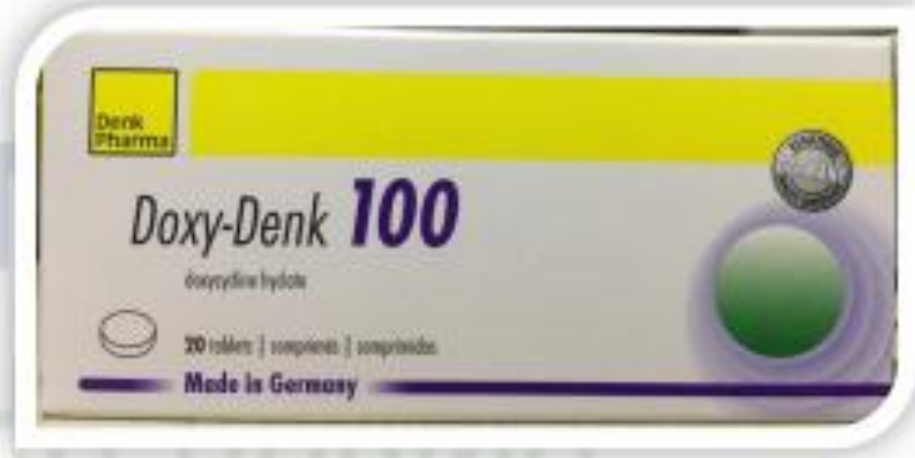


Tetra-cyclines

- **Main drugs:** **Tetracycline - Demeclocycline**
  Doxycycline - Minocycline.

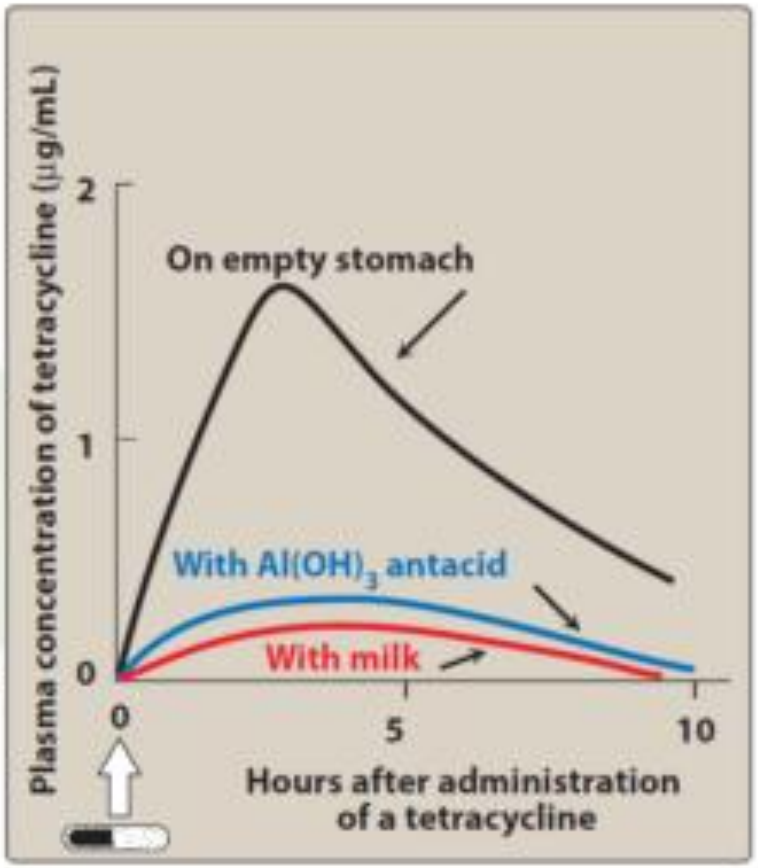
Broad-spectrum, act against types of (Gram + and -) bacteria. But there is an increasing resistance against this family.





Pharmacokinetics notes:

- **Absorption:** decreased significantly by divalent and trivalent ions **(Fe^{2+}, Fe^{3+}, Ca^{2+}, Mg^{2+}, Al^{3+} or Zn^{2+}).**
- Doxycycline is less affected than the others.

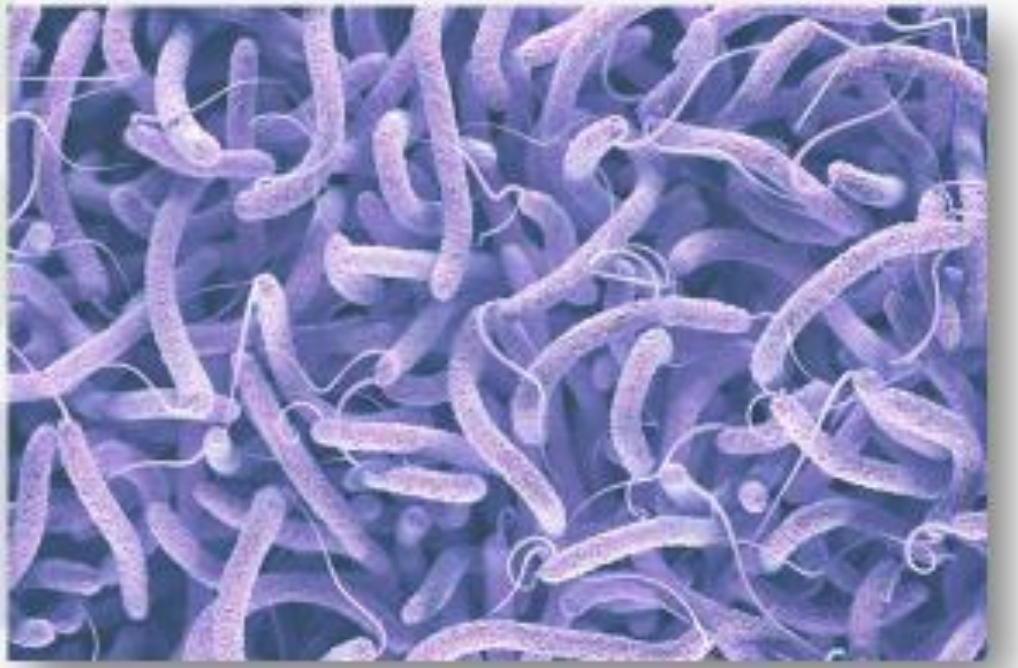


- **Distribution:** Doxycycline and minocycline are highly lipo-philic → well-distributed in skin and cerebro-spinal fluids (CSF).

Excretion: Doxycycline is excreted by liver → used for patients of renal failure.

Doxycycline is the best drug in this family, and it is used to treat:

1) Cholera.



2) Chlamydia and syphilis.

3) Lyme disease.

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4) Acute bacterial sinusitis.

5) Refractory UTIs.

6) Acne.

7) Pneumonia due to **Mycoplasma pneumoniae**.

8) Listeriosis.

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9) Prophylaxis of malaria.

10) Adjuvant to quinine in treatment of malaria.

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11) Skin infections (effective against community-acquired MRSA).

Main adverse effects:

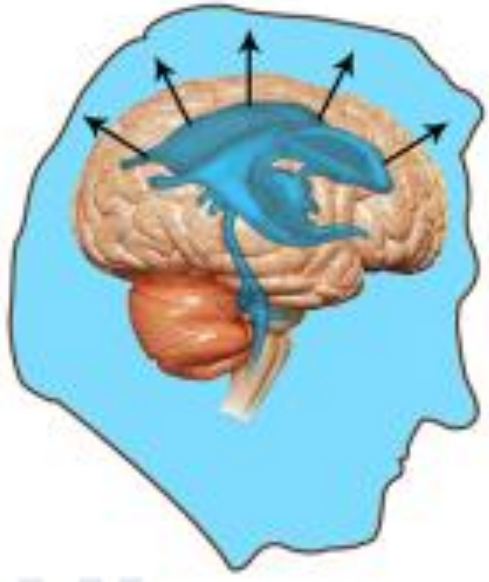
1) Deposition in the bones and teeth, especially in:

- Fetus → so this family is contraindicated in pregnant women).
- Children → so contraindicated in children < 8 years (USA - Australia - WHO) **or** < 12 years (UK).

Exception: Tetracycline ophthalmic ointment 1% can be used even for neonates.

2) Hepato-toxicity: especially in pregnant women and those with preexisting hepatic dysfunction or renal impairment **(which tetracycline can be used in normal dose in patients of renal failure ??).**

3) Photo-toxicity: occurs more frequently with tetracycline and demeclocycline. Exposure to sun or UV rays may lead to severe sunburns → Patients should wear adequate sun protection.



4) Intracranial hypertension (headache and blurred vision) may occur rarely in adults → Stop drug immediately (Tetracyclines are contraindicated with Isotretinoin).

5) Because tetracyclines are **irritant to esophagus**, all of tetracyclines should be:

- Taken with plenty of water.
- On sitting or standing.
- And patient must not lie down for 30-60 min.

6) Fanconi syndrome (when a tetracycline is expired) → **nephrotoxicity**.

7) Vestibular dysfunction (doxycycline & minocycline) → **nephrotoxicity**.

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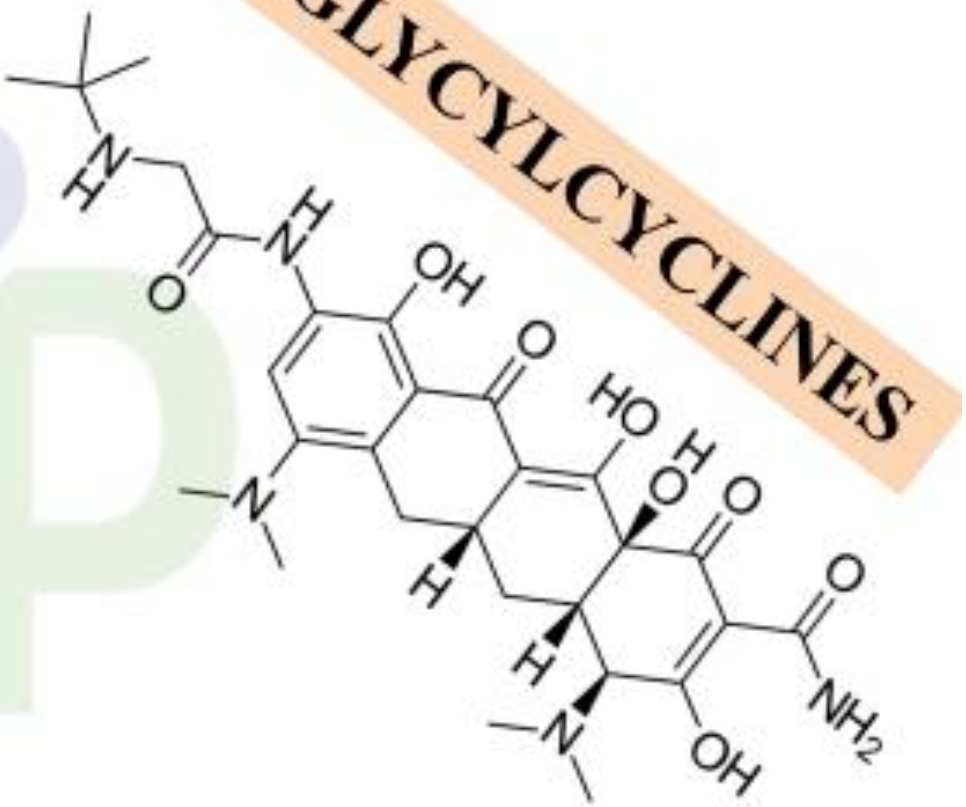
GLYCYLCYCLINES

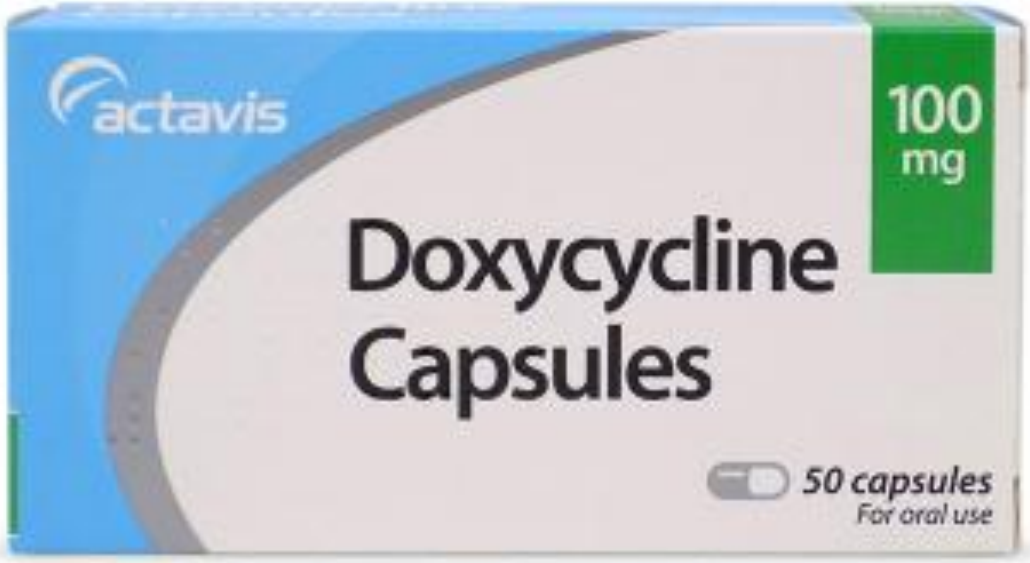


Tigecycline is a derivative of minocycline. It is very effective against (Gram + bacteria) including MRSA & VRE. So it is used to treat complicated skin infections.

- High volume of distribution → low plasma conc. → **a poor option** for blood stream infections.

Tetracyclines & Pregnancy

Tetracyclines are **teratogenic** (disrupt fetal bones and teeth).



Some allow using tetracyclines for pregnant women **in the 1st 16 weeks** of pregnancy (limited scientific evidence).

Tetracyclines & Breastfeeding:

- Theoretically, the milk's calcium prevents absorption of tetracyclines.
- Practically, **Tetracycline** and **Doxycycline** can be used for ≤ 10 days.

(Also **Minocycline**, but it may give the human milk a **black color**).

Tetracyclins & Food

1) General:

- **Tetracycline** and **demeclocycline** should be used on an empty stomach hour before food or 2 hours after it), but with a large amount of water.

- **Doxycycline** and **minocycline** can be taken on a full stomach.

2) Specific: all tetracyclines must be separated from the following ions:

(Fe^{2+}, Fe^{3+}, Ca^{2+}, Mg^{2+}, Al^{3+} or Zn^{2+}).

Notice that **dairy products** are rich in calcium. Drugs must be taken 2 hours before ions or 2-4 hours after them

Macrolides

- **Main drugs:** **Erythromycin- Clarithromycin - Azithromycin - Roxithromycin - Spiramycin.**

- Broad-spectrum, act against types of (Gram + and -) bacteria.

Pharmacokinetics notes:

- **Absorption:** Erythromycin is acid-labile. So it can be used as:

  1) Enteric-coated tablets (Eythromycin **Base**).

  2) Esters (pro-drugs) that are acid-stable:

  Erythromycin **stearate**.

  Erythromycin **ethyl-succinate**.

  Erythromycin **estolate**.

- **Distribution:** Erythromycin passes to the prostatic fluids → can be used for prostatitis.

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- **Main uses:**

1) Good alternatives to β-lactams in treatment of RTIs.

2) **Azithromycin** is used for diphtheria. **Erythromycin** may be used as a pro-kinetic agent → in treatment of gastroparesis or postoperative ileus.

2) **Clarithromycin** is used (in combination) to treat H. pylori.

3) **Azithromycin** is used in treatment of chlamydia and mycoplasma.

4) **Spiramycin** is used for toxoplasmosis during pregnancy (especially when the pregnant women is diagnosed before the 18th week of pregnancy).

5) **Roxithromycin** is used for RTIs and skin infections.

Main adverse effects:

1) GIT upset: may occur with all of macrolides, especially with erythromycin → take oral macrolides with food or a large amount of water **(see macrolides and food).**

2) Hepato-toxicity and jaundice: may occurs with all of macrolides, especially with erythromycin → especially **estolate** ester → especially in pregnant women.

3) Oto-toxicity: associated with azithromycin and high doses of erythromycin → may lead to deafness (may be reversible or irreversible).

4) Cardiac arrhythmia (QT prolongation).

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5) Many drug-drug interactions

(erythromycin and clarithromycin > azithromycin).

Telithromycin: is similar to azithromycin, but it is stronger on many types of resistant bacteria.

Macrolides & Pregnancy

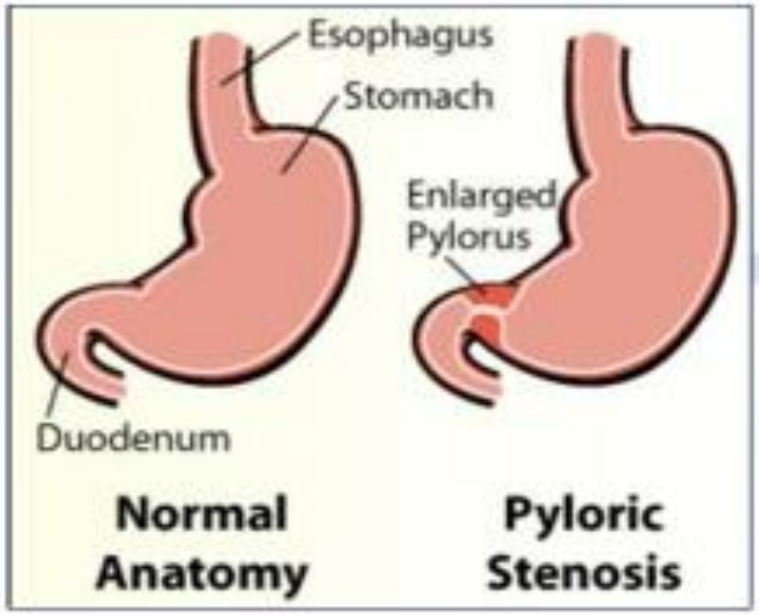
- **Erythromycin base, stearate, ethyl-succinate & lactobionate** can be used (but **estolate** salt is contraindicated during pregnancy due to the increased risk of hepatotoxicity).

- **Azithromycin** can be used.
- **Clarithromycin** is not recommended (toxic in animals) !!
- **Roxithromycin** is controversial !!

Macrolides & Breastfeeding:

In the 1st 7 weeks of the infant life, macrolides may ↑ risk of "Pyloric stenosis" → avoid macrolides. If necessary, **azithromycin** is the safest.

- After the 1st 7 weeks of the infant life, **erythromycin, clarithromycin and azithromycin** can be used.



Macrolides & Food

- **Erythromycin stearate, erythromycin base (non-enteric coated),** and **azithromycin cap** should be used on an empty stomach (1 hour before food or 2 hours after it), but with large amount of water.

- **Erythromycin ethyl-succinate** should be used on a full stomach.

- **Erythromycin base (enteric coated), erythromycin estolate, azithromycin tablets or susp, clarithromycin** and **spiramycin** can be used without regard to food.

Lincosamides

- **Main drugs:** **Lincomycin - Clindamycin.**

- Narrow-spectrum, act against types of (Gram +) bacteria, including streptococci, staphylococci and MRSA. Also they are active against anaerobic bacteria.

Main uses of clindamycin:

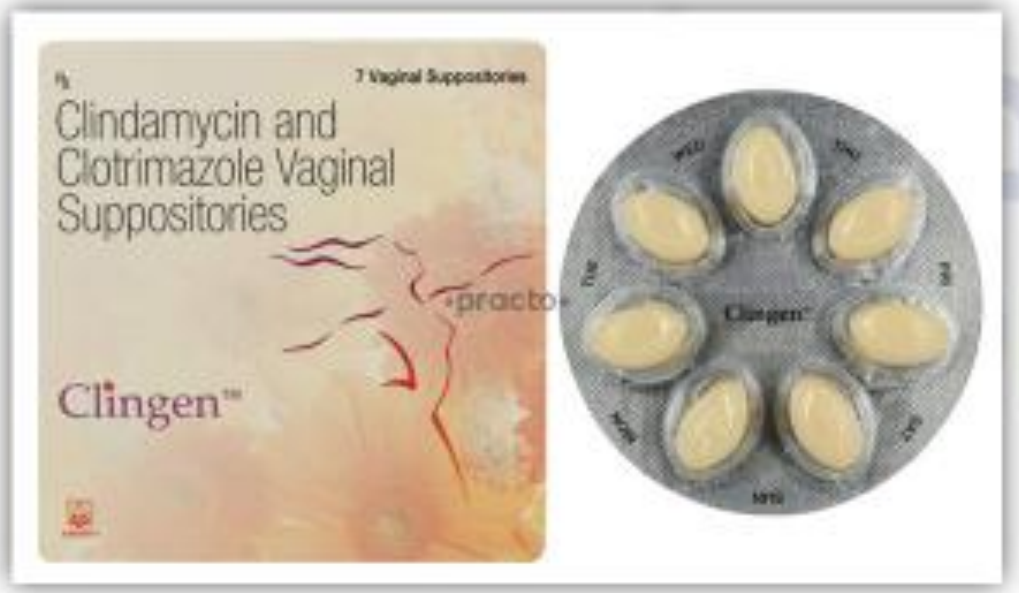
1) Skin infections and surgical prophylaxis.

2) Dental infections and surgical prophylaxis of infective endocarditis.

3) Bacterial vaginosis.

4) Streptococcal pharyngitis (in penicillin-allergic patients).

5) Acne (topical clindamycin only).



Main adverse effects:

1) Antibiotic-associated diarrhea and pseudo-membranous colitis (may be fatal).

2) Skin rash.

Lincosamides & Pregnancy

Clindamycin can be used (**lincomycin** is an alternative) but without **benzyl alcohol** !!

Lincosamides & Breastfeeding:

Clindamycin may be used if necessary (but the other alternatives are preferred, because clindamycin has a relative high risk for causing diarrhea in the infant. Diarrhea may be **bloody**).

- Clindamycin **topically** or **intra-vaginally** can be used safely.

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Lincosamides & Food

Oral clindamycin can be used without regard to food. It is **irritant to the esophagus**, so it should be:

- Taken with plenty of water.
- On setting or standing.
- Patient mustn't lie down for 30 minutes

Others:

1) Chloramphenicol:

- Broad-spectrum, act against types of (Gram + and -) bacteria.
- Because of the high systemic toxicity (aplastic anemia), it is used only in life-threatening infections for which no alternatives exist.
- Usually used **topically** for eye infections.

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- If used in **neonates**, it may cause the **Gray Baby Syndrome:**

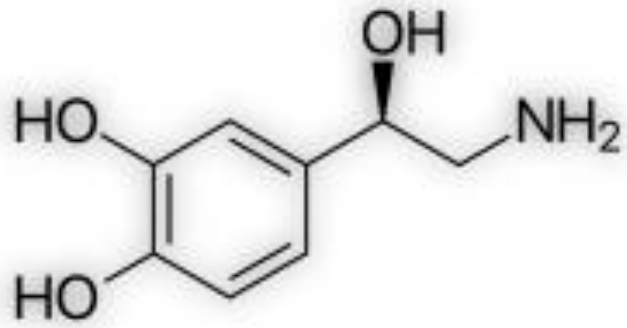
Neonates have immature liver → can't metabolize chloramphenicol → accumulation of drug in their bodies → ↓ breathing and CVS collapse → cyanosis.

2) Linezolid:

- Active against (Gram +) bacteria, including MRSA and VRE.
- Used for severe infections, like skin infections and nosocomial pneumonia.
- Oral suspension should be gently mixed (without shaking).
- Tablets and suspension can be taken **without regard to food.**

Used during **pregnancy** and **breastfeeding** (without stopping it) **only when necessary** (limited data).

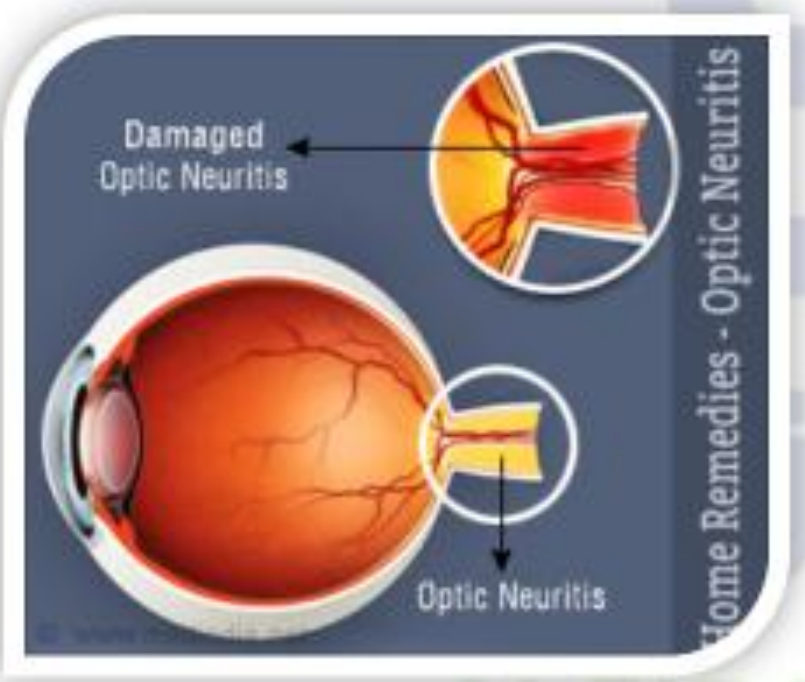
Adverse effects of Linezolid:



1) ↑ Blood pressure (because it inhibits MAO enzyme, monitor).

2) Hypoglycemia (monitor).

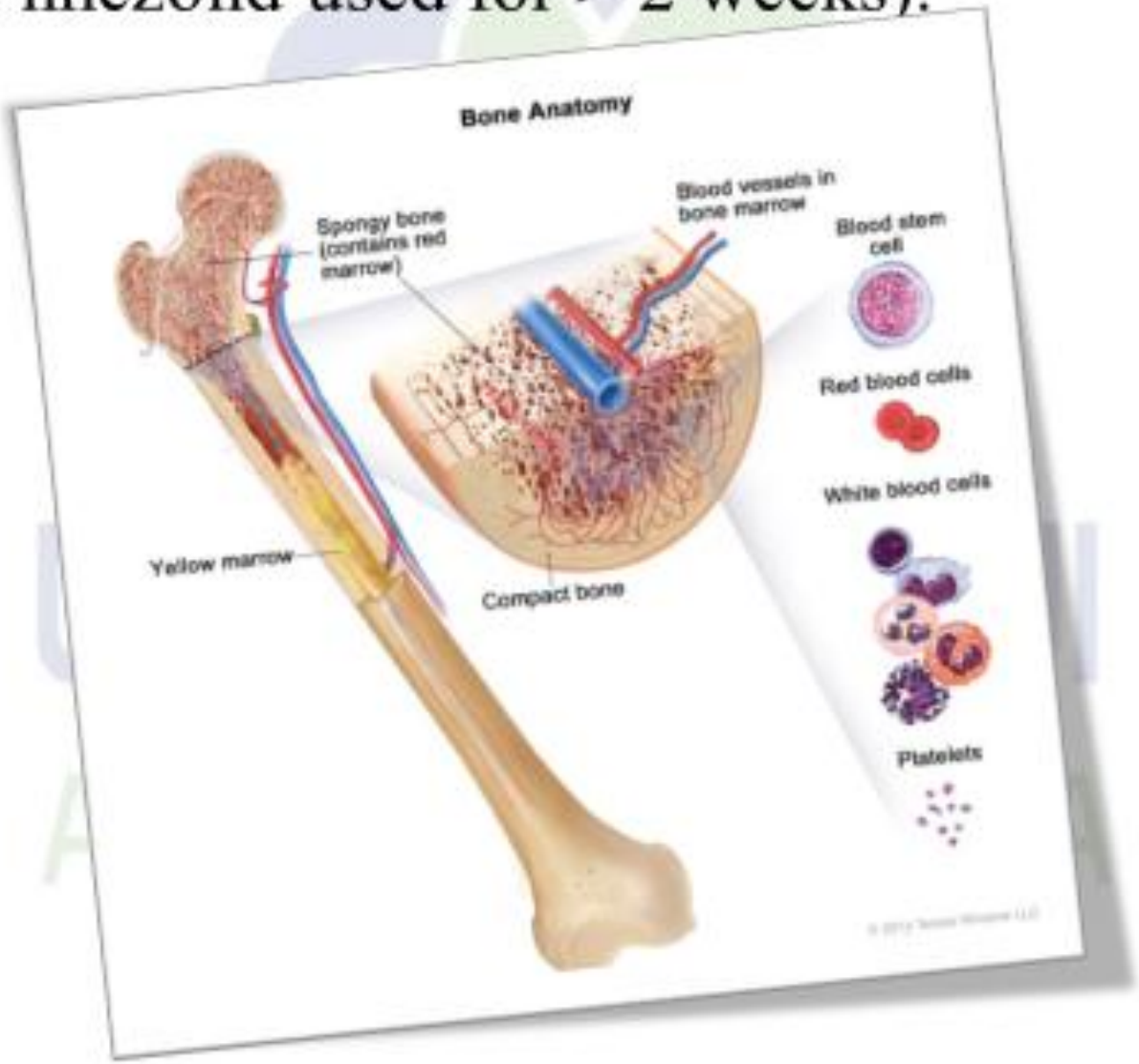
3) Peripheral and optic neuropathy, thought to be because of inhibition of mitochondrial protein synthesis (usually if used for > 28 days) that may lead to blindness → go **immediately** to an ophthalmologist immediately if have "blurred vision, visual field defect, changes in color vison".



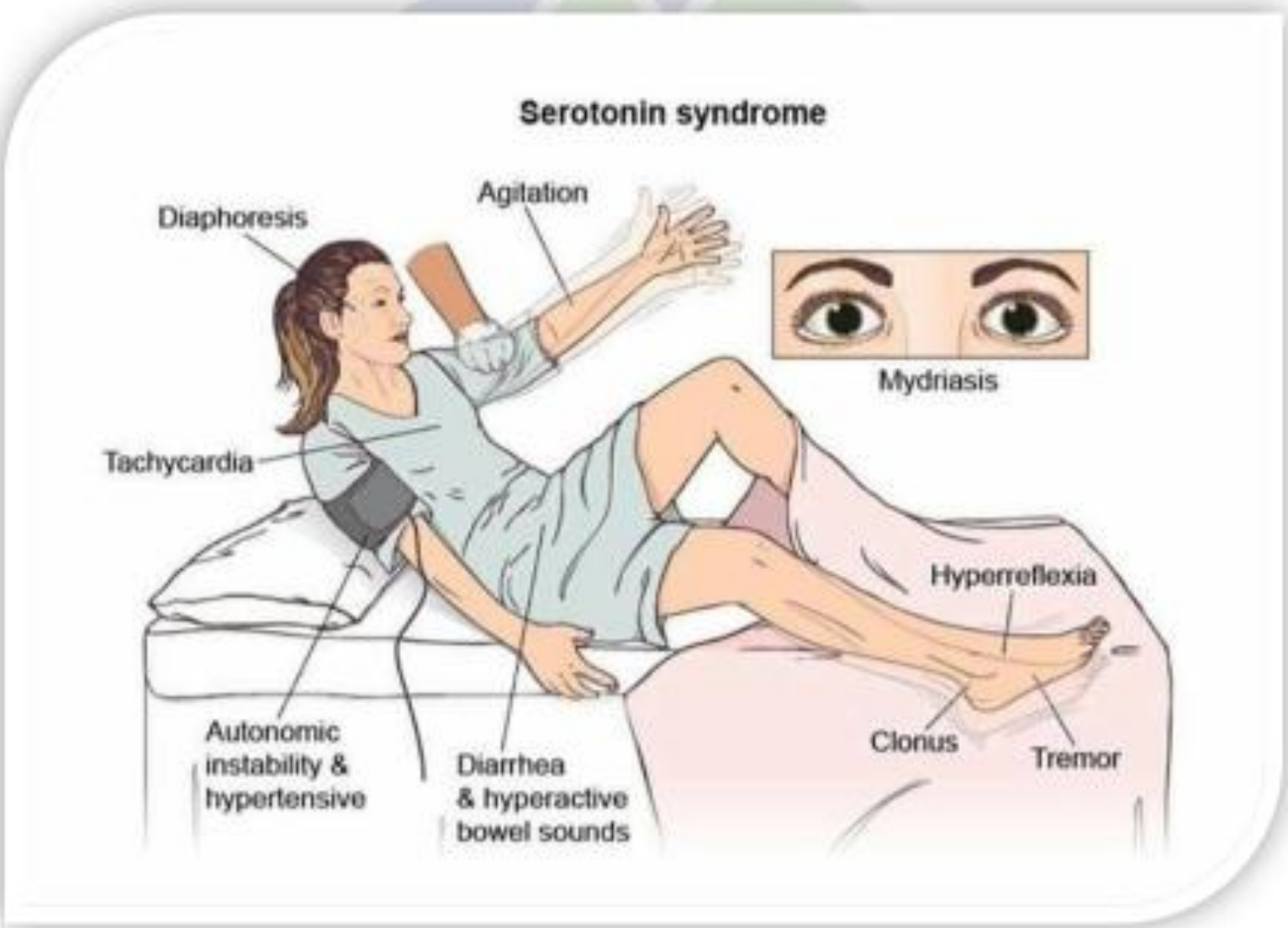
4) Lactic acidosis (mitochondrial effect) → monitor symptoms & treat immediately.

5) Myelosuppression (reversible):

Anemia, leukopenia (neutropenia), thrombocytopenia or pancytopenia → monitor CBC at baseline then every week (specially if linezolid used for > 2 weeks).



6) Serotonin syndrome, if used with other drugs increasing serotonin (e.g. SSRIs, TCAs, triptans, dextromethorphan).



7) Facilitates seizures.

8) Hyponatremia (post-marketing), leading to confusion, somnolence, generalized weakness, or even respiratory failure and death → monitor serum sodium especially in elderly people and diuretic-users.

3) Fusidic acid (Sodium fusidate):

- Active against Staphylococci, including MRSA.
- Used for skin infections (wounds - burns).
- Used usually in combination with other antibiotics (to ↓ bacterial resistance).
- Can be used **topically** for pregnant and breastfeeding women (but keep the infant without a direct contact with the drug).

- **When used orally:** Sodium fusidate has a much better absorption → used in lower doses.

Mupirocin has the same **activity** of fusidic acid (not the same **safety**).

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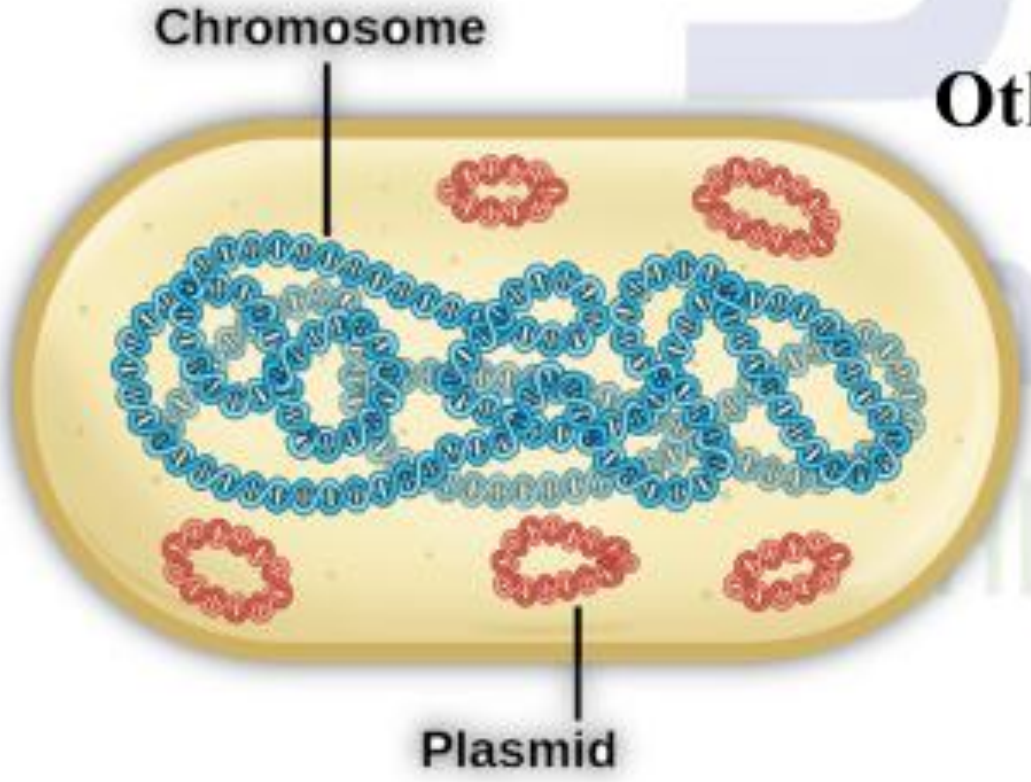
Nucleic acid-synthesis Inhibitors

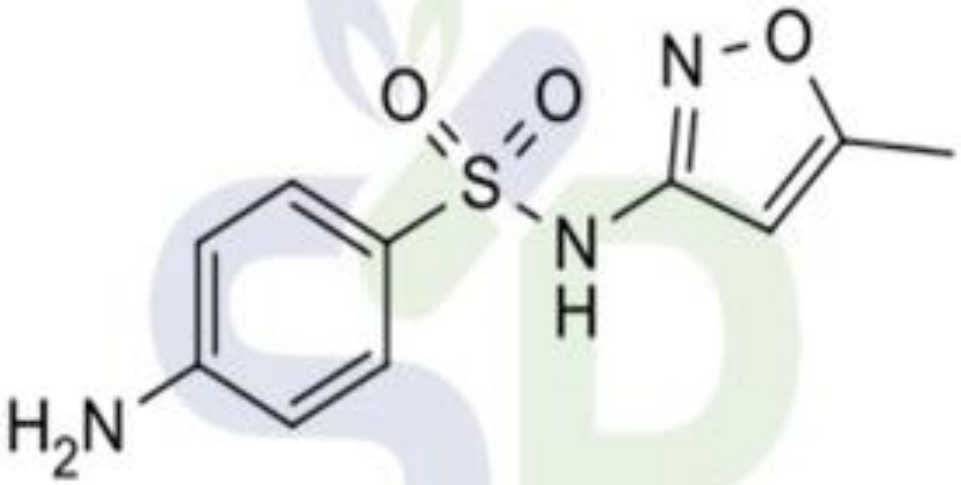
Sulfonamides

Quinolones

Others



Sulfon-amides:



Oral absorbable drugs:

- Sulfamethoxazole.
- Sulfadiazine.
- Sulfadoxine.

Oral non-absorbable drugs:

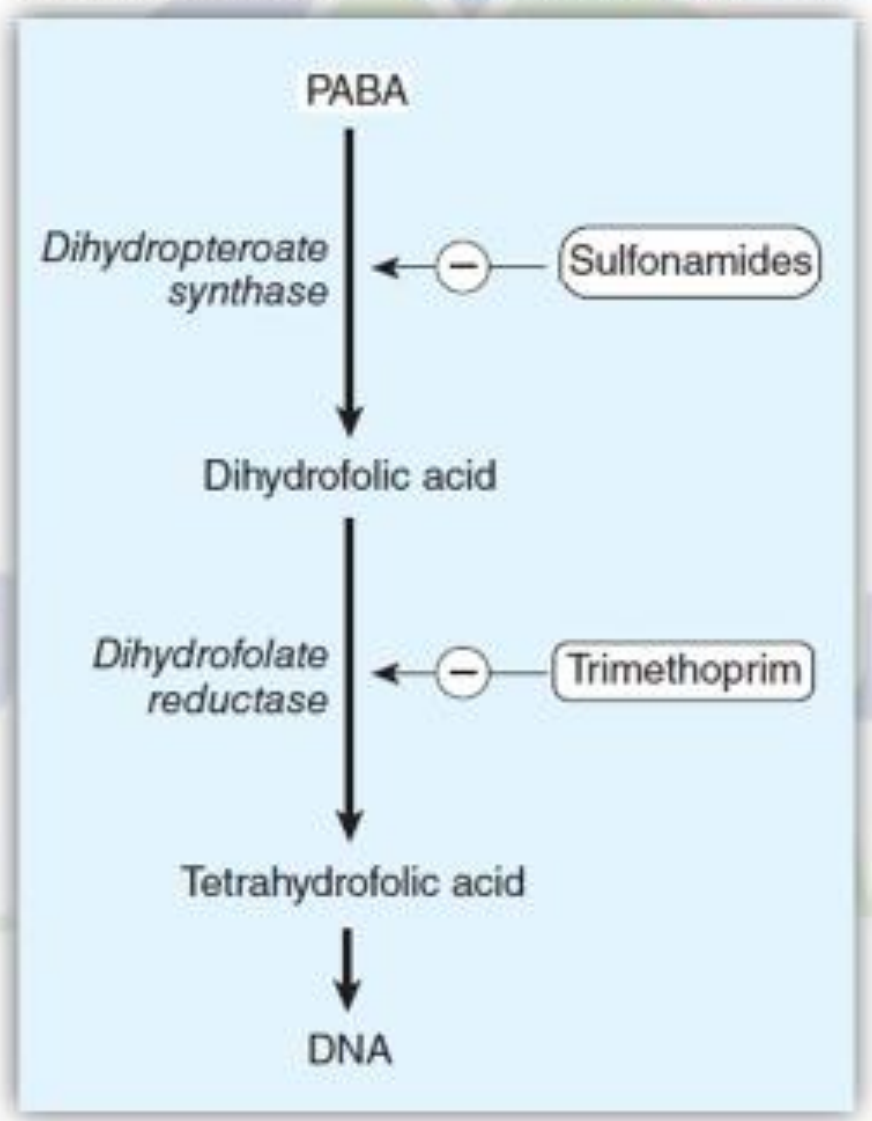
- Sulfasalazine.
- Mesalazine (Mesalamine).

Topical drugs:

- Mafenide acetate.
- Silver sulfasalazine.
- Sulfacetamide.

M.O.A:

- Sulfonamides prevent conversion of PABA (Para-Amino-Benzoic Acid) to Dihydro-folic acid → no Tetrahydro-folic acid → no DNA → inhibit bacterial replication → **Bacterio-statics.**



- Broad-spectrum, act against types of (Gram + and -) bacteria. But there is an increasing resistance against this family

Main uses:

1) Oral absorbable drugs:

- Sulfamethoxazole + trimethoprim → used for **UTIs** and **bacterial diarrhea**, **meningitis** and **skin infections** (including community-acquired MRSA).

Co-trim-oxazole

- Pyrimethamine + sulfadiazine → used for treatment of toxoplasmosis.

- Pyrimethamine + sulfadoxine → used for treatment of malaria.

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2) Oral non-absorbable drugs: used orally to act topically on GIT:

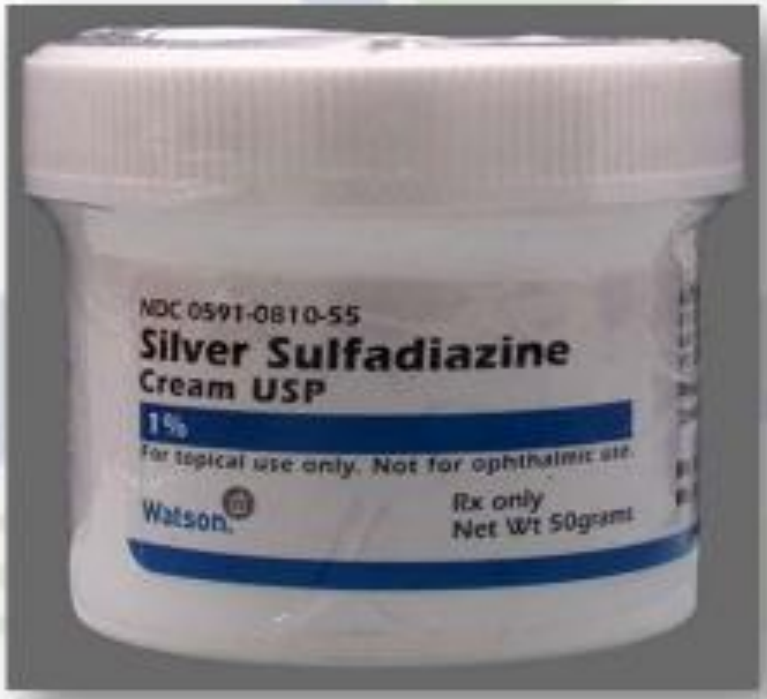
- Sulfasalazine and mesalazine (mesalamine) → used for treatment of inflammatory bowel disease (IBD), because they are antibiotics and they ↓ inflammation.

3) Topiacal drugs:

- Sulfacetamide → used topically for treatment of bacterial conjunctivitis.

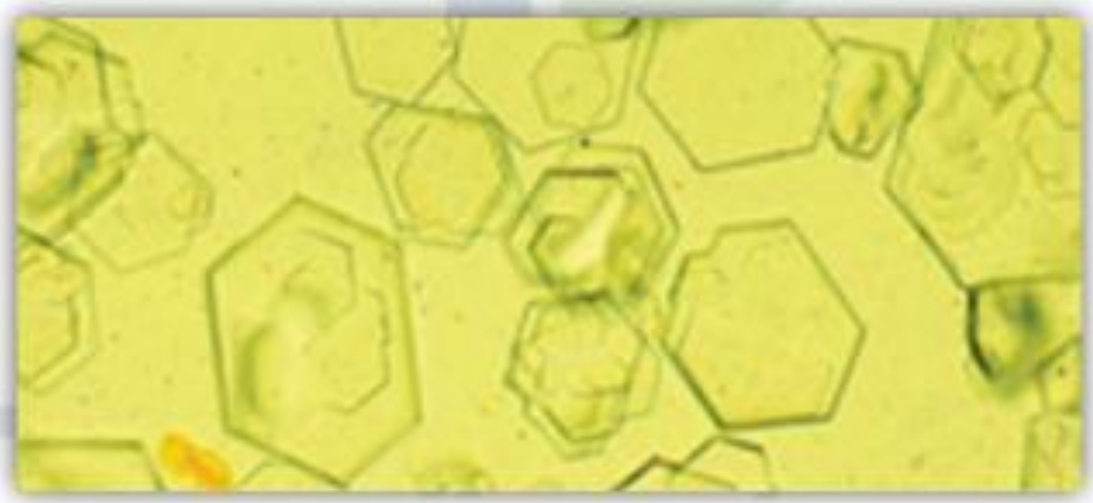
- Mafenide acetate → used topically for 2nd and 3rd degrees of burns (but has more absorption and more side effects).

- Silver sulfadiazine → used topically for 2nd and 3rd degrees of burns (but has less absorption and less side effects).



Adverse effects of Sulfonamides:

1) Crystalluria: because sulfonamides precipitate in the acidic or neutral medium → advise patient to drink a lot of water daily. Also we can use NaHCO3 to convert urine to a basic medium.



2) Hypoglycemia, especially in patients of D.M, renal impairment and AIDS.

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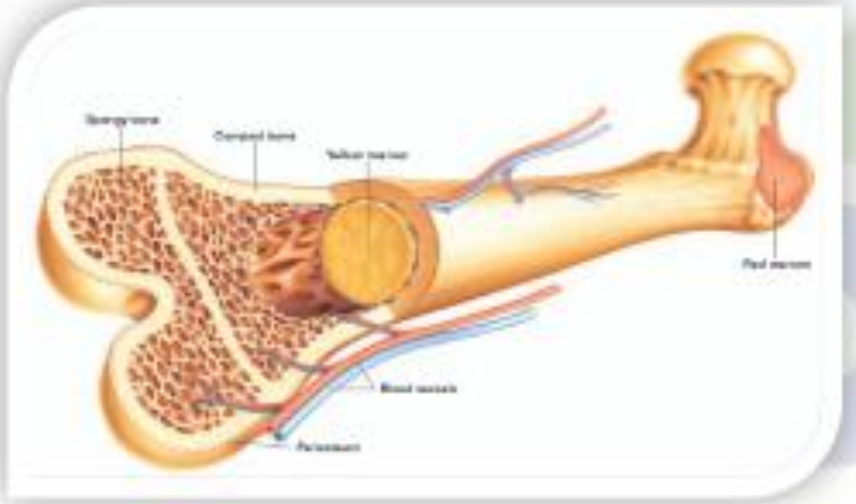
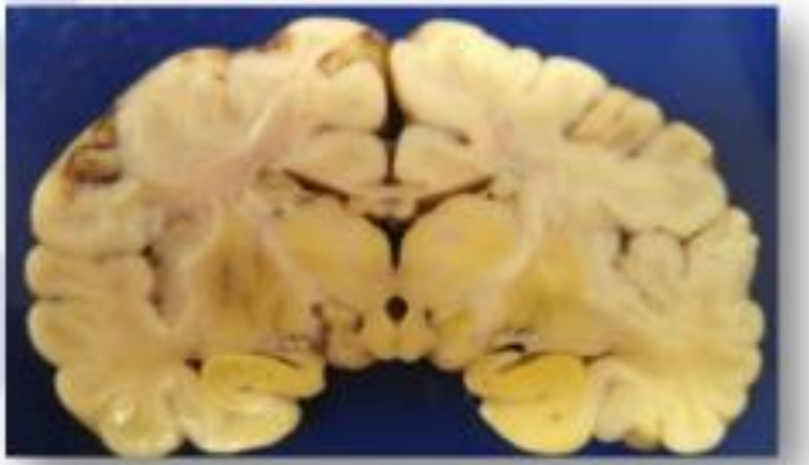
3) Hematologic disturbances:

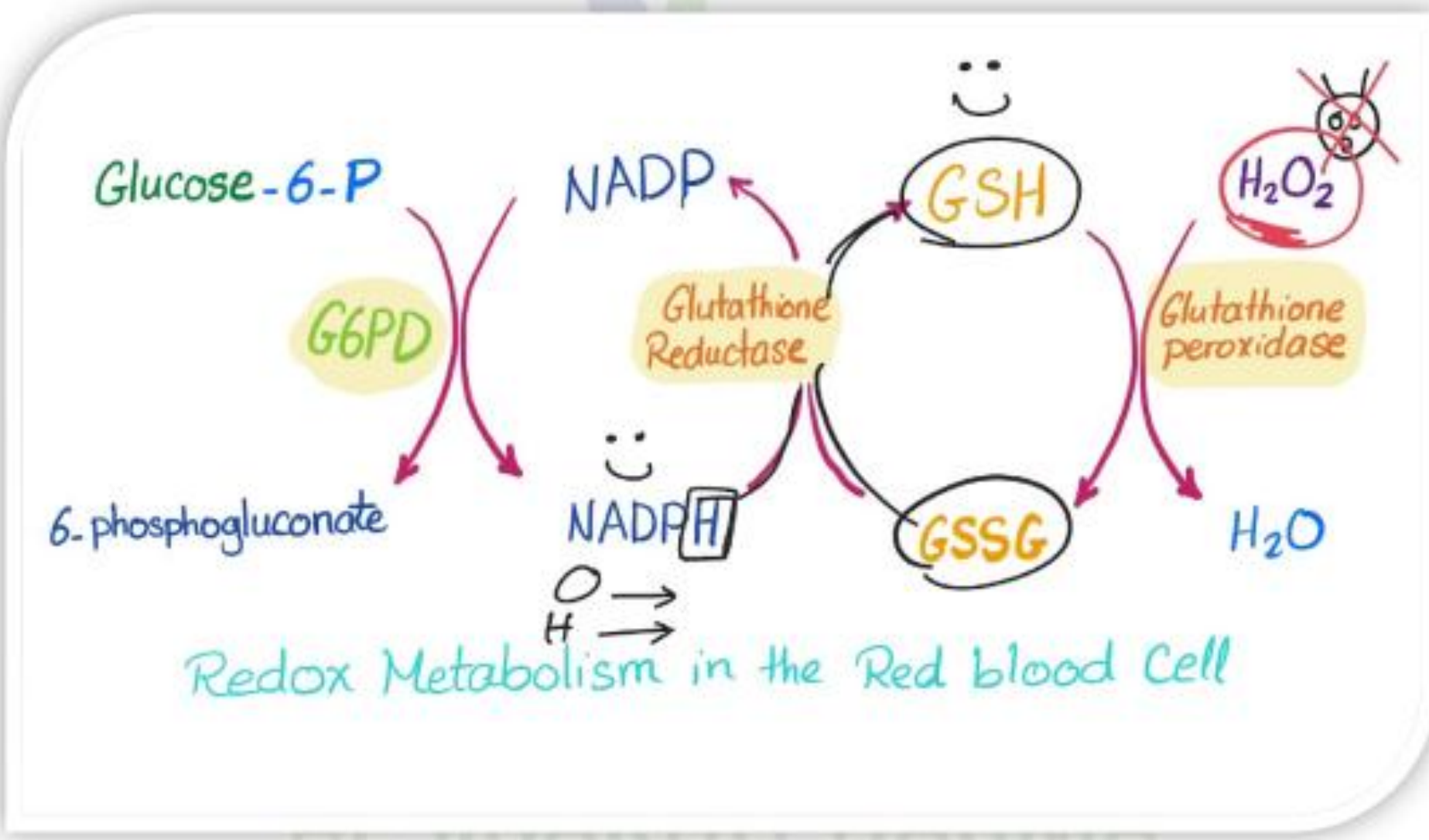
- Aplastic anemia or thrombocytopenia.
- Hemolytic anemia in patients of G6PD deficiency.





5) Strong binding to albumin:

- May displace other drugs → drug-drug interactions.
- May displace bilirubin → If used in children < 2 months old may lead to **Kernicterus** **(sulfonamides are contraindicated in children** < 2 months old).


Glucose-6-P
NADP
GSH
H_2O_2
G6PD
Glutathione Reductase
Glutathione peroxidase
6-phosphogluconate
NADPH
GSSG
H_2O
Redox Metabolism in the Red blood Cell

Sulfonamides & Pregnancy

- Sulfonamides are generally **not recommended**, because of their **anti-folate** activity.

- When **absolutely necessary**:

1) Add **folic acid** **(5 mg/day)** along with the sulfonamide.

2) If used in the 3rd trimester → monitor the neonate for **hemolytic anemia** & **methemoglobinemia.**

Sulfonamides & Breastfeeding:

Co-trimoxazole (sulfamethoxazole + trimethoprim) & "silver sulfadiazine topically" can be used if :

1)The infant is healthy.
2) The infact's **age** is > 1 month after full-term pregnancy.
3) The infant has neither **jaundice** nor **G6PD** (because sulfonamides may cause kernicterus or hemolysis, respectively).

Sulfonamides & Food

Co-trimoxazole (sulfamethoxazole + trimethoprim), **sulfasalazine, sulfadoxine/pyrimethamine** should be used on a full stomach, with large amount of water.

Quinolones :

First generation:

- Nalidixic acid.
- Cinoxacin.

Second generation:

- Ciprofloxacin.
- Ofloxacin.
- Norflocxacin.
- Lomefloxacin.

Third generation:

- Levofloxacin.
- Gatifloxacin.

Fourth generation:

- Moxifloxacin.

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M.O.A:

- Quinolones inhibit topoisomerase II (DNA gyrase) and topoisomerase IV enzymes → inhibit DNA separation and destruct DNA → **Bactericidals.**

Main uses:

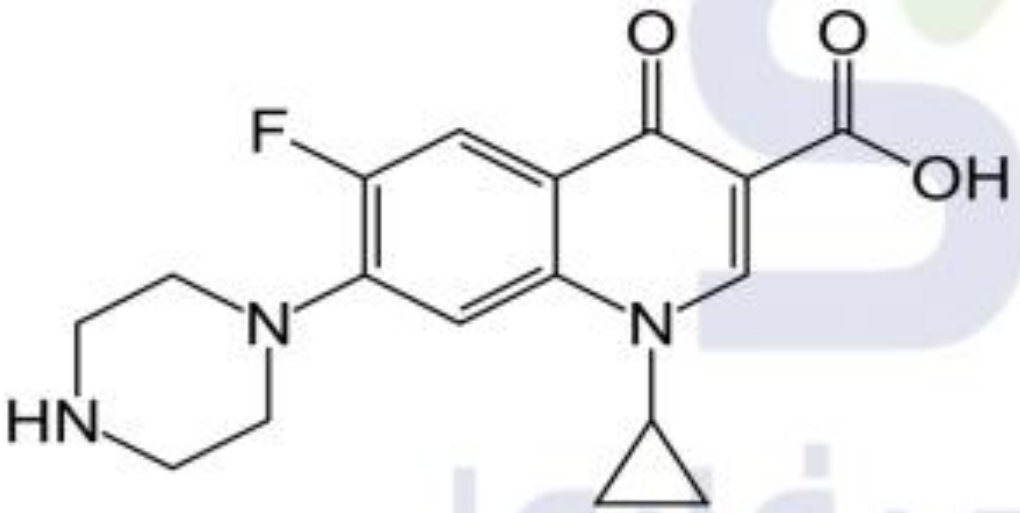
1) First Generation: Nalidixic acid - Cinoxacin:

- Active against some (Gram-) bacteria → used for uncomplicated cystitis in women. Also may be used for bacterial diarrhea (but this generation is weak).

The following generations contain "Fluorine atom" so called **Fluoro-quinolones**:

2) Second generation: Ciprofloxacin - Ofloxacin - Norflocxacin:

- Active against types of (Gram+ and -) bacteria → used for UTI, prostatitis and bacterial diarrhea. **Ciprofloxacin** is also used for typhoid fever, and used topically for bacterial conjunctivitis.



3) Third generation: Levofloxacin - Gatifloxacin

- Levofloxacin is active against types of (Gram+ and -) bacteria → used for UTI, prostatitis, bacterial diarrhea, skin infections, respiratory tract , and H. pylori.
- Both drugs are used topically for bacterial conjunctivitis.

Levofloxacin and **Moxifloxacin** are called **"Respiratory Fluoroquinolones"**

4) Fourth generation: Moxifloxacin:

- Moxifloxacin used for respiratory and skin infections but ***not*** used in UTIs (because its concentrations in urine are low).

Adverse effects of Quinolones:

1) **Cardiac arrhythmia** (QT-prolongation), especially **Moxifloxacin**.

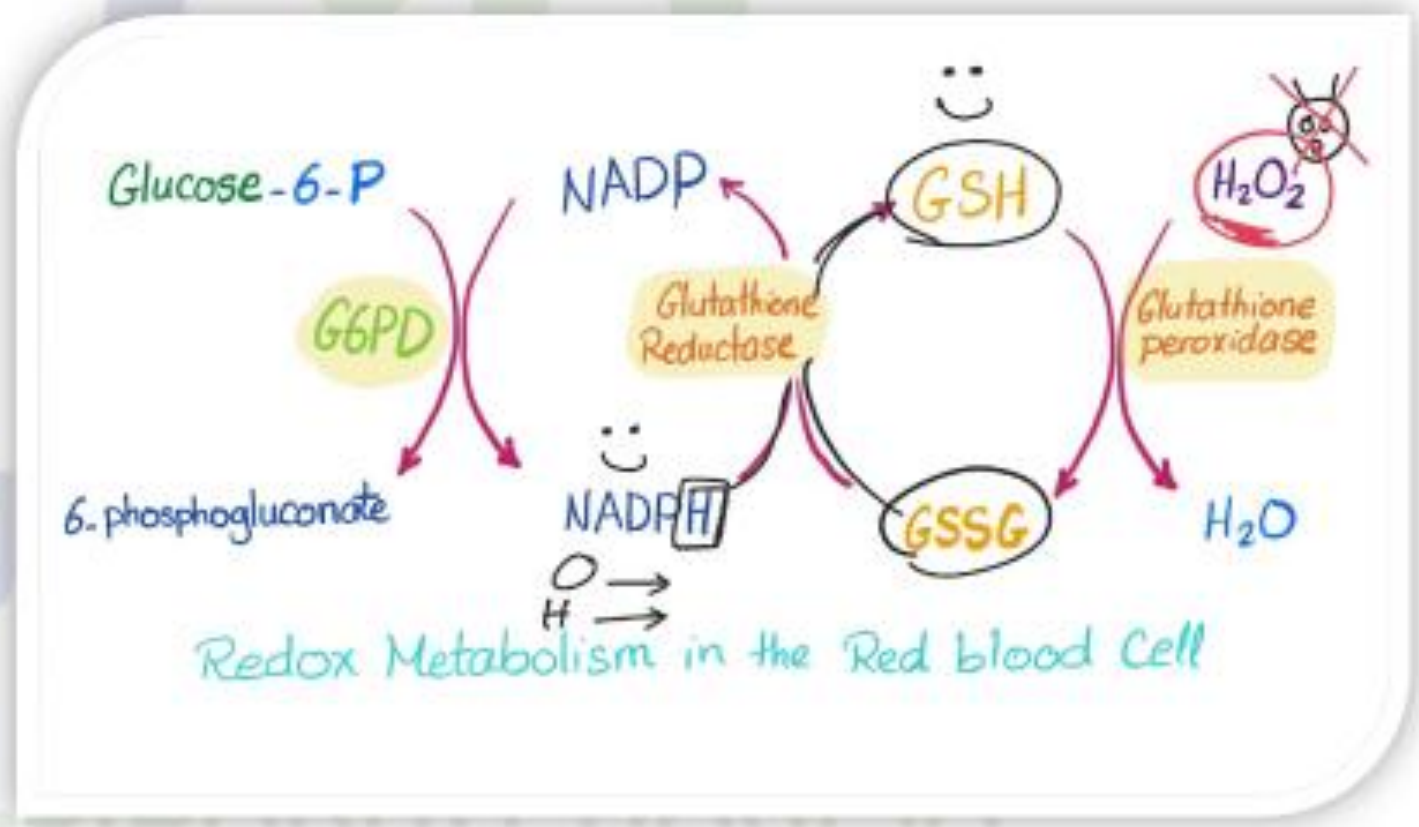
2) **Facilitate seizures** in patients of epilepsy.

3) **Hypoglycemia** (or hyperglycemia) in patients of D.M.

4) Photo-toxicity.

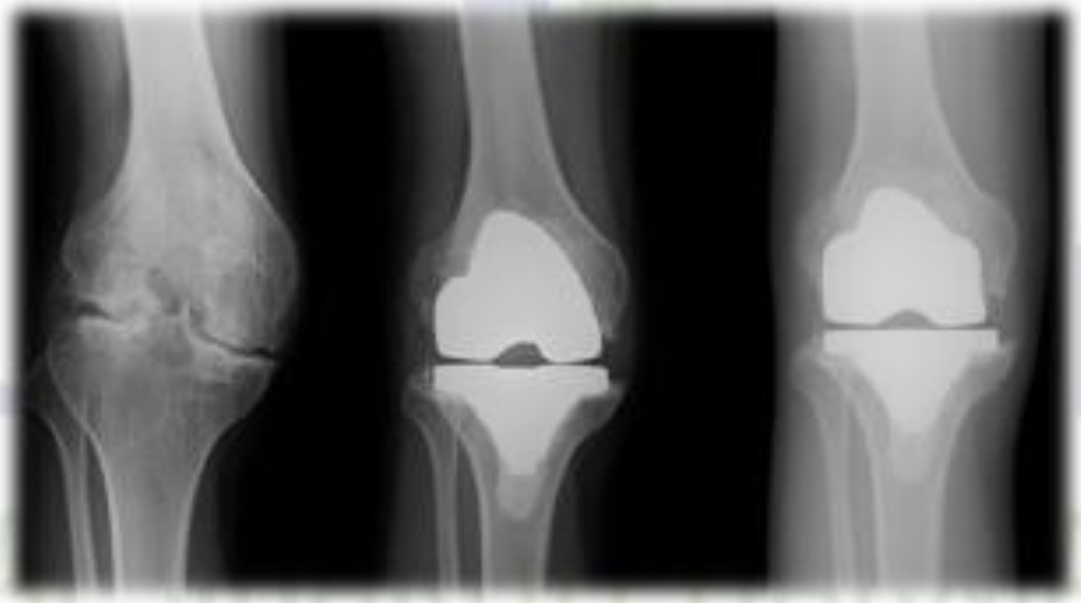
5) Hemolytic anemia in patients of **G6PD deficiency**.

Phototoxicity



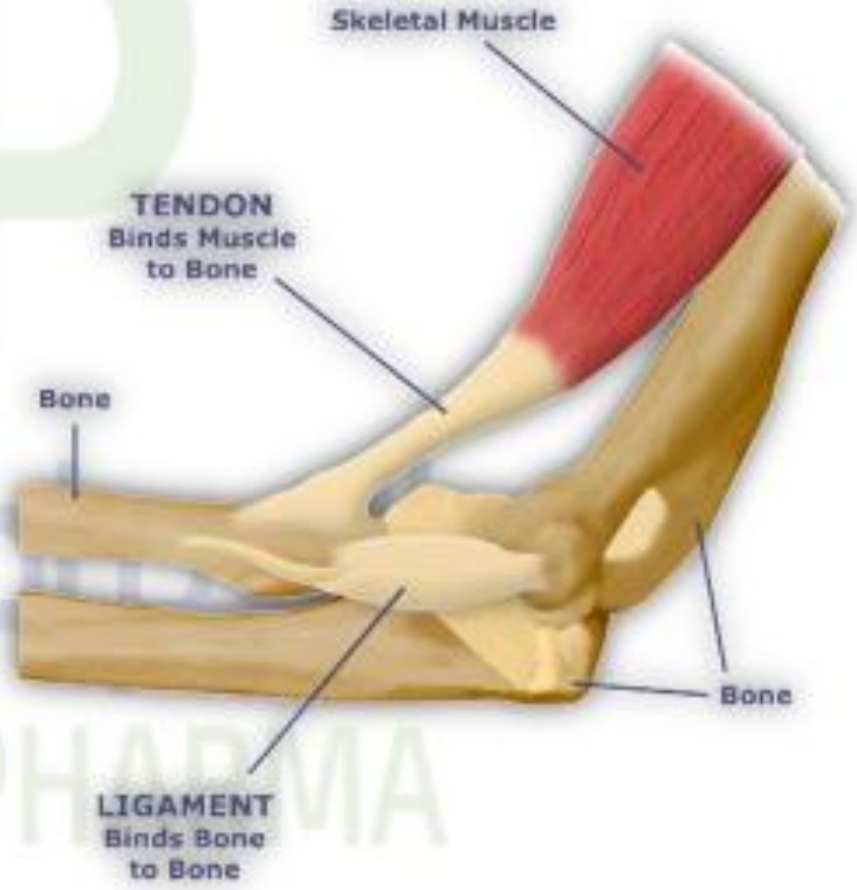
6) Arthro-pathy: based on animal studies, it may occur with the use of **fluro-**quinolones in:

- Fetus.
- Children < 18 years old. But if necessary, we can use them especially ciprofloxacin (more clinical trials).



7) Tendinitis or tendon rupture especially in:

- Patients > 60 years old.
- Patients using systemic corticosteroids.



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Quinolones & Pregnancy

- Quinolones are generally not recommended, because of their toxicity in **animal studies.**

- Some human data suggest safety of these drugs, especially **Nalidixic acid**).

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Quinolones & Breastfeeding:

Theoretically:

The milk's calcium prevents absorption of fluoro-quinolones.

Practically:

a) If the infant suffers from **epilepsy**, **cardiac disease, jaundice** or **G6PD-deficiency** → avoid all quinolones.

b) If not → use **nalidixic acid, ciprofloxacin or ofloxacin** (more safety data).

Norfloxacin, **levofloxacin** and **moxifloxacin** also can be used (preferred to be used immediately after breastfeeding).

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Quinolones & Food

1) General:

- Fluoroquinolones are preferred to be taken on empty stomach, especially norfloxacin (why ??)

2) Specific: **must** be separated from the following ions:

(Fe^{2+}, Fe^{3+}, Ca^{2+}, Mg^{2+}, Al^{3+} or Zn^{2+}).

Notice that **dairy products** are rich in calcium

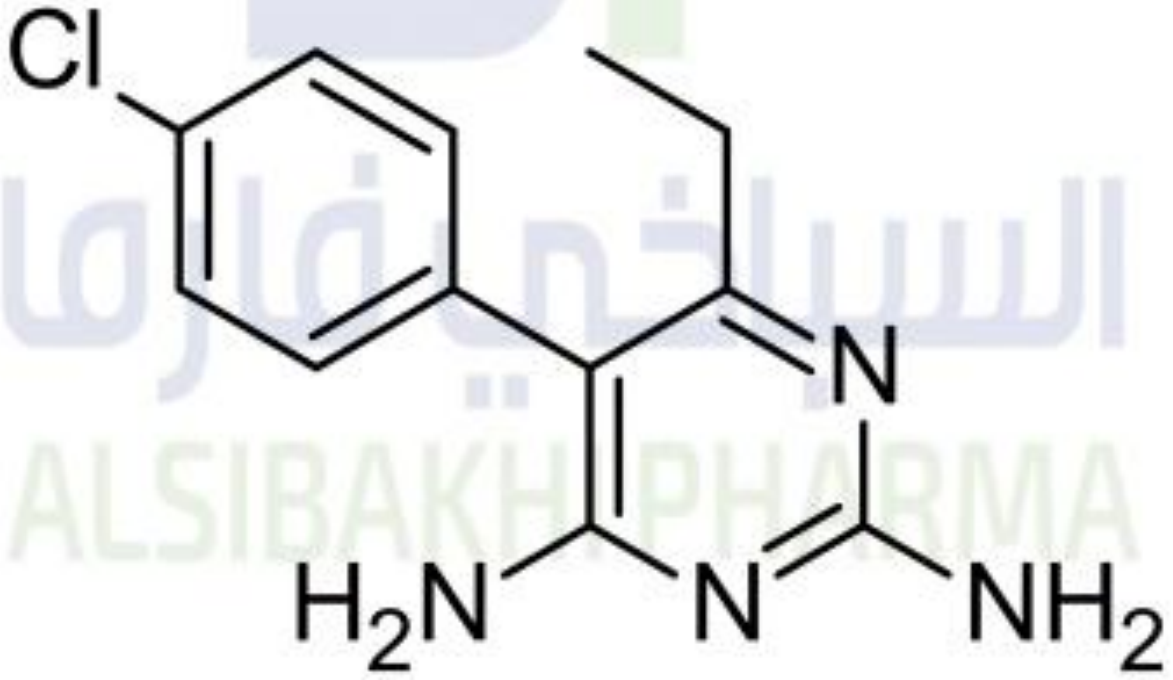
Drugs must be taken **2 hours before** ions or **2-4 hours after** them (but **Moxifloxacin** must be taken 4 hours before ions or 8 hours after them).

Others:

1) Pyrimethamine:

- M.O.A is similar to sulfonamides.

Used in combination with sulfonamides to treat malaria and toxoplasmosis (as previously discussed).



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2) Nitrofurantoin:

- M.O.A is damage of the bacterial DNA (the exact mechanism is unknown).
- Used for uncomplicated cystitis in women.
- Should be used in a full stomach (to decrease GIT upset).

- **Pregnant women:** is contraindicated in pregnant patients at term (37 weeks of gestation), during labor and delivery → may cause hemolytic anemia in the neonate.
- **Breastfeeding women:** same to co-trimoxazole.

Methenamine (Hexamine) :

- **M.O.A:** Hydrolyzes in the acidic urine to formaldehyde **(antibacterial for cystitis, and cannot be resisted).**

Hexamine (alone) can be used in pregnant women and breastfeeding women.

Nitrofurantoin and **Hexamine** are called **"Urinary anti-septics"**

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